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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

MEDICAL DEVICES ADVISORY COMMITTEE

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NEUROLOGICAL DEVICES PANEL

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March 12, 2010
8:00 a.m.

Hilton Washington DC North
620 Perry Parkway
Gaithersburg, Maryland

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ROBERT HURST, M.D.	Panel Chair
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DAVID GOOD, M.D.	Temporary Voting Member
RALPH PETRUCCI, ED.D.	Temporary Voting Member
FREDERICK G. BARKER, II, M.D.	Temporary Voting Member
JULIAN PAOLICCHI, M.D.	Temporary Voting Member
HARRY CHUGANI, M.D.	Temporary Voting Member
JEROME ENGEL, JR., M.D.	Temporary Voting Member
MERCEDES JACOBSON, M.D.	Temporary Voting Member
KENT NEW, M.D.	Temporary Voting Member
MICHAEL PRIVITERA, M.D.	Temporary Voting Member
NIRJALESHWAR KUMAR NIKHAR, M.D.	Temporary Voting Member
BERNARD RAVINA, M.D.	Temporary Voting Member
CAROLYN PETERSON	Consumer Representative
MICHAEL HALPIN	Industry Representative
DEBORAH FALLS, MPH	Designated Federal Officer
JAMES SWINK	Designated Federal Officer

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OPEN PUBLIC HEARING SPEAKERS:

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DENNIS SPENCER, M.D., Yale University, American Epilepsy Society
TROY GIBSON
JENNIFER GIBSON
SHANNON BAGY
JACQUELINE MILLER
TINA NICHOLS
TETHIA LONGWORTH

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M E E T I N G

(8:00 a.m.)

DR. HURST: I would like to call this Neurological Devices Advisory Panel to order.

I'm Dr. Robert Hurst, the Acting Chairperson of the Panel. I'm an interventional nerve radiologist and vascular neurologist from the University of Pennsylvania.

At this meeting, the Panel will be making a recommendation to the Food and Drug Administration on the premarket approval application of P960009 for the Deep Brain Stimulation System for Epilepsy. This device is indicated for bilateral anterior thalamic nucleus stimulation using the Medtronic DBS System for epilepsy. The DBS System is indicated as an adjunctive therapy for reducing the frequency of seizures in individuals diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to antiepileptic medications.

If you haven't already done so, please sign the attendance sheets that are at the registration tables by the doors.

If you wish to address this Panel during one of the open sessions, please provide your name to Ms. Ann Marie Williams at the registration table. If you're presenting in the open public session and have not previously provided an electronic copy of your presentation to the FDA, please arrange to do so with Ms. Williams.

I note for the record that the voting members present constitute a quorum as required by 21 C.F.R. Part 14. I would like also to add that the Panel participating in the meeting today has received training in FDA device law and regulations.

Before we begin, I would now like to ask our distinguished Panel members and FDA staff seated at this table to introduce themselves. Please state your name, your area of expertise, your position and affiliation, and let's start to my left.

DR. EYDELMAN: Good morning. My name is Malvina Eydelman, and I'm Director of the Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices at the FDA.

DR. NIKHAR: Good morning. My name is Nirjal Nikhar. I'm a neurologist in Maryland.

DR. PRIVITERA: Michael Privitera, Professor of Neurology at the University of Cincinnati, and I head the Epilepsy Center.

DR. JACOBSON: Mercedes Jacobson, Temple University, Philadelphia.

DR. EVANS: Scott Evans, Department of Biostatistics, Harvard University.

DR. NEW: Kent New. I'm a neurosurgeon at St. Vincent's Medical Center in Jacksonville, Florida.

DR. PETRUCCI: Ralph Petrucci, neuropsychologist, Drexel University College of Medicine in Philadelphia.

MR. SWINK: James Swink, Designated Federal Officer for the Center of Devices and Radiological Health at the FDA.

MS. FALLS: Deborah Falls, the Designated Federal Officer for this Panel.

DR. ENGEL: Jerome Engel, Jr. I'm Director of the UCLA Seizure Disorder Center.

DR. GOOD: Good morning. David Good, Professor and Chair in Neurology at Penn State University.

DR. BARKER: Fred Barker, neurosurgeon from Massachusetts General Hospital.

DR. PAOLICCHI: Julian Paolicchi, Associate Professor of Pediatrics in Neurology from Vanderbilt University, Director of Pediatric Epilepsy and Pediatric Neurology.

DR. CHUGANI: Harry Chugani, Professor of Pediatrics and Neurology. I head the Epilepsy Surgery Program at Children's and also Child Neurology and the Positron Imaging Center.

DR. RAVINA: I'm Bernard Ravina. I'm a neurologist and Director of the Movement Disorders Unit at the University of Rochester.

MS. PETERSON: I'm Carolyn Peterson. I'm the Consumer Representative. I work at Mayo Clinic in Rochester, Minnesota, and my background is in exercise physiology and medical informatics.

MR. HALPIN: My name is Mike Halpin. I'm the Industry Rep today, and I work for Genzyme Corporation in Regulatory Affairs.

DR. HURST: Deborah Falls, the Designated Federal Officer for this Panel, will make some introductory remarks.

MS. FALLS: Good morning. I will read into the record two Agency statements prepared for this meeting, the Conflict of Interest Statement and the Appointment of Temporary Voting Members Statement.

The Food and Drug Administration is convening today's meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the Industry Representative, all members and consultants of the Panel are special Government employees or regular Federal employees from other agencies and are subject to Federal conflict of interest laws and regulations.

The following information on the status of this Panel's compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in today's meeting and to the public. The FDA has determined that members and consultants of this Panel are in compliance with Federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's services outweighs his or her potential financial conflict of interest. Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the committee essential expertise.

Related to the discussion of today's meeting, members and consultants of this Panel who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and, for purpose of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts/grants/CRADAs; teaching/speaking/writing; patents and royalties; and primary employment.

For today's agenda, the Panel will discuss, make recommendations, and vote on a premarket approval application supplement for the Deep Brain Stimulation System for Epilepsy sponsored by Medtronic, Inc. This device is indicated as adjunctive therapy for reducing the frequency of seizures in individuals diagnosed with epilepsy. For this device, a patient's epilepsy should be characterized by partial-onset seizures affecting only a part of the brain when they begin, with or without secondary generalization, that are refractory to antiepileptic medications.

Secondary generalization is used to describe a partial-onset seizure that later spreads to the whole brain. Refractory to antiepileptic medications means that patient's epilepsy does not respond to approved medications.

Based on the agenda for today's meeting and all financial interests reported by the Panel members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Robert Hurst and Dr. Bernard Ravina.

Dr. Hurst's waiver addresses his employer's interest in the sponsor's study. His institution is identified as a study site. Dr. Hurst has no involvement in the study and receives no funding, but his employer was awarded between 101,000 and 300,000 dollars for the duration of a contract from 2004 to 2010. In the upcoming year, his institution will receive payments between 0 and 50,000 dollars for patient follow-up and pending study reports.

Dr. Ravina's waiver involves his employer's interest in a competitor's product study. His institution is identified as a study site. Through the period of the contract, his employer was awarded between 101,000 and 300,000 dollars. Dr. Ravina has no involvement with the study and received no funding. Although the actual amount is unknown for payments over the next year, it is estimated that his employer would receive between 0 and 50,000 dollars.

The waivers allowed these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents which are posted on the FDA's website at www.fda.gov/advisorycommittees/default. Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 6-30 of the Parklawn Building. A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Michael Halpin is serving as the Industry Representative, acting on behalf of all related industry, and is employed by Genzyme Corporation.

We would like to remind members and consultants that if the discussions involve any other products and firms not already on the agenda for which a FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all participants to advise the Panel of any financial relationships that they may have with any firms at issue. Thank you.

I will now read appointment to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated

October 27, 1990, and amended August 18, 2006, I appoint the following individuals as voting members of the Neurological Devices Panel for the duration of this meeting on March 12, 2010: Scott R. Evans, Ph.D.; David Good, M.D.; Robert Hurst, M.D.; Ralph Petrucci, ED.D.; Jerome Engel, M.D.; Mercedes Jacobson, M.D.; Kent New, M.D.; Michael Privitera, M.D.; Dr. Nikhar, M.D.; and Bernard Ravina, M.D. For the record, these individuals are special government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting.

In addition, I appoint Robert Hurst, M.D., to act as a temporary Chairperson for the duration of this meeting. This was signed by Jeffrey E. Shuren, M.D., J.D., Director of Center for Devices and Radiological Health, and dated February 27, 2010.

Before I turn the meeting back over to Dr. Hurst, I would like to make a few general announcements

Please make a note of the following announcements.

Transcripts of today's meeting will be available from Free State Court Reporting. The telephone number is (410) 974-0947. Information on purchasing videos of today's meeting can be found on the table outside the meeting room.

I would also like to take the time to introduce our FDA press contact, which is Peper Long. I would like to remind everyone that members of the public and press are not permitted in the Panel area at any time during the meeting, including breaks. If you are a reporter and wish to speak to FDA officials, please wait until after the Panel meeting has ended.

In order to help the transcriber identify who is speaking, please be sure to introduce yourself each and every time you do speak.

Finally, as a courtesy to those around you, please silence your electronic devices if you have not already done so. Thank you very much.

DR. HURST: We will begin with the FDA updates. The first will be the Division update by Dr. Malvina Eydelman.

DR. EYDELMAN: Good morning. I would like to bring your attention to the recent reorganization of the Office of Device Evaluation. As of January 2009, this is what the Office of Device Evaluation looked like with the Division of Ophthalmic and Ear, Nose and Throat Devices and Division of General Restorative and Neurology Devices being two of the five divisions.

As of February 1, 2009, all of the neurological devices were transferred to our division. Subsequently, the Division of Ophthalmic and Ear, Nose and Throat Devices has changed its name. We are now the Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices.

Unfortunately I don't have time to introduce all of my staff. However, I did want to take a few minutes to give you an overview of our new division structure.

I have two outstanding Deputies, Dr. Eric Mann and Dr. Kesia

Alexander, who is minding shop back in the office.

Deborah Falls is our Associate Director and is acting as a DFO for today.

Quynh Hoang is the Branch Chief of Neurodiagnostic and Neurotherapeutic Devices Branch.

Kwame Ulmer is the official Branch Chief for Ophthalmic Lasers, Neurostimulators and Diagnostic Branch. He's on detail, and Mr. Brad Cunningham is the current acting Branch Chief.

Dr. Tina Kiang is the Branch Chief for the Intraocular, Cornea and Neuromaterials Branch.

And Dr. Srinivas Nandkumar is the Branch Chief for the Ear, Nose and Throat Branch.

So in accepting all of the neurological devices into the division, there was a distribution of neurological devices among the four branches, and with NNDB or Neurodiagnostic and Neurotherapeutic Device Branch being responsible for all of the neuro-manual surgical instruments, evoked response devices, EEGs/MEGs, neurovascular devices, deep brain and spinal cord stimulators, transcranial magnetic stimulators, and hypo/hyperthermia devices.

Our ONDB Branch is in charge of ophthalmic diagnostic and surgical devices, brachytherapy and retinal implants, electrical nerve stimulators, RF lesion devices, neuro lasers, interferential current therapy devices, and ECT devices.

ICNB is in charge of all of the intraocular lenses, corneal implants, viscoelastics, corneal storage media, adhesives, contact lenses, cranioplasty, dural sealants, and dura mater substitutes.

ENTB, in addition to taking care of the ENT Devices, handles peripheral and vagal nerve stimulators, neuro endoscopes, auditory evoked response devices, stereotaxic drills and burrs.

I'm delighted to report that since reorganization, we have been able to retain and recruit outstanding review staff. The names of all of the reviewers are on this full division org chart. However, as I said, due to the time limitations, I will not go through all of the names, but I'm delighted to report that we have a very, very strong review team that from now on will handle all of the neurological devices.

As of 7/09, the Division and the office has moved to a new facility in White Oak. This is the division phone number should you have any questions, and my e-mail as well is on this slide.

Thank you. That completes the Division update.

DR. HURST: Thank you, Dr. Eydelman.

Dr. Danica Marinac-Dabic, from the Office of Surveillance and Biometrics, will provide a postmarket update.

DR. MARINAC-DABIC: Good morning, Dr. Hurst, Dr. Eydelman, distinguished members of the Panel, and also members of the audience.

I would like to provide a brief update on the CDRH's Post-Approval Studies Program, and I would like to accomplish two goals, number one, to clearly state the message that we take the Panel recommendations very seriously as we design and follow the conduct of the post-approval studies that you as the Panel members might recommend during your Panel deliberations. Number two, I wanted to also give you a brief update on where the Center is going in terms of advancing the infrastructure and methodologies for better design of post-approval studies.

First, I would like to provide a brief context with regard to CDRH postmarket science. If you can look at the left side of the slides, I would like to represent here the FDA mandated studies. These are the studies that FDA can ask at the time of the PMA approval or anytime during the postmarket phase. If there is a signal that had been identified and more information is needed, we can ask the sponsor to conduct the study to address the specific question.

On the other side, we have FDA-sponsored studies that are typically designed to address more overarching issues related to class of the devices, and also they're designed to build the methodologies and better infrastructure to study the performance of medical devices.

Also, as an overarching initiative, you see on this slide a Sentinel Network Initiative, and I am sure that many of you are familiar with this initiative that will give the FDA the opportunity to have access to point of care data that is currently collected in various distributed networks, and by accessing those data, we might be able to reach better scientific decisions throughout our total product life cycle.

As part of Sentinel Network, certainly the development of methodologies is a big piece because we would like to take a lead and certainly help our colleagues from industry to offer the better methodologies for designing the post-approval studies.

Now, let's go back to the post-approval studies, and I know that you have received the training, and you probably already heard this, but I would like to again reiterate that FDA and CDRH can ask for continuing evaluation and reporting on the safety and effectiveness and reliability for devices for its intended use.

FDA also has another authority to request what we call postmarket surveillance studies or Section 522 studies anytime after the product had been cleared or approved if there is a specific question that needs to be addressed and if those devices fall into one of these four categories: failure of the device, reasonably likely to have serious adverse health consequences; expected to have significant use in pediatric populations; that are implanted for longer than one year; or if the device is life-supporting or life-sustaining used outside of user facility.

We certainly understand why we are asking for post-approval studies. We cannot rely for all the answers to come from the postmarket clinical trials, and many of the postmarket clinical trials are not designed to address questions that can be only addressed in the postmarket setting; such as, for example, long-term performance of medical devices or real-world device performance or effectiveness of training programs may not be necessarily best addressed in the postmarket settings, or the subgroup performance would be another reason why we would ask for post-approval study.

And these post-approval studies have really great public health value as the product moves from the postmarket setting to the real-world utilization.

The post-approval studies contribute to better design of postmarket studies because we feedback the information that we learn in the postmarket setting to our premarket colleagues in the Office of Device Evaluation and Office of In Vitro Diagnostics.

The post-approval studies can detect real-time signals that can be actionable certainly and help us identify overarching regulatory science needs in CDRH.

During the last several years, we have undertaken robust transformation of the postmarket programs at CDRH. In 2005 we have established the post-approval studies program. The post-approval study review functions, before that time, resided in premarket review divisions in ODE and OIVD. We consolidated this into one program in 2005 and began raising scientific rigor of post-approval studies, clearly requesting the clear objective for the post-approval studies, hypothesis, sample size based on the hypothesis, clear timelines, and we developed also the tracking system for the post-approval studies that we request.

So all of the studies are tracked through an electronic system, and we also have a public website that we created in 2007 that shares the information with the public.

In 2007 we started a series of updating Advisory Panels on the progress these studies are making.

In 2008 we initiated BIMO inspections of post-approval studies, meaning that our BIMO colleagues now are going out and inspecting those studies that are done under the condition of approval authority.

And in 2008 and 2009, we have increased our focus on infrastructure building for post-approval studies and focused also on methodological development to help us design better studies.

This is the link to CDRH's website that went live in April of 2007, and this is what this website looks like. It's a link to our PMA database, and one can search and find out information about the original approval order and the status of the post-approval study. We provide the information that is not confidential, that can be shared with the public, and we are certainly looking for ways to actually increase the amount of information that we can share with the public in order to be more transparent with regard to this program.

We also reach out to the clinical community and the manufacturers' community and other stakeholders. These are the two recently sponsored FDA workshops conducted last year, one focused on implementation strategies for post-approval studies, another focused on methodological approaches for post-approval studies.

Now, I would like to give you just a snapshot of how many post-approval studies we currently have. As you can see from 2005 to 2009, what's represented here in blue is the number of approved original PMAs and panel-track supplements, and what's presented in red is the number of the ones that had a post-approval study requirement at the time of the approval.

Very often when we ask for the post-approval study, we ask for more than one study per PMA order, and that's represented on this slide.

This is how these studies are progressing. Approximately 19 percent of our ongoing studies is not progressing well. The rest of the studies have progress adequate status, and we certainly are working very closely with manufacturers to make sure that the studies that are not progressing well are put back on track.

This is how the post-approval studies for neurological devices are doing. As you can see, from 2005 through 2009, this is how many PMA and panel-track supplements for neurological devices have been approved and how many studies had been requested.

And, again, this is the progress of neurological post-approval studies, and most of the studies are progressing fine. There is one study that has a status that's not adequate.

Now, in the last two minutes, I would like to give you an idea where the Center is moving with regard to the post-approval studies. We certainly place much more emphasis on the registries and as an important public health tool to address postmarket questions, and perhaps nesting the post-approval studies in them. And I would like to give you just some examples of already ongoing registry efforts that CDRH is taking important role in. These are listed here. I'm not going to take much of your time going through every one of them, but it's important to say that we use existing registries for post-approval studies, and it's important to know that as you discuss the post-approval studies and how they're going to be conducted.

Also, we facilitate new registry development, and here are some of the examples. We work closely with clinical societies to develop the national infrastructure for nesting the post-approval studies and addressing the postmarket questions.

These are again some examples of how we are using existing registries for our discretionary studies, and we have a number of ongoing contracts with ACC, with Society of Thoracic Surgeons, with Kaiser, with Cornell, and even outside the United States some registries. And we explore registries' capabilities for active surveillance and through the linking studies with Medicare claims data.

Finally, one important project that I would like to share with you is our expanding initiative through cooperation with Harvard and Professor Sharon-Lise Norman, who is our lead investigator on a project that will develop the methods and certainly develop the models that will quantify the progressing ability of those models to pull multiple data sources and give us better understanding of how medical devices are performing. Currently the FDA's operating under the paradigm that the silos of information exist in various parts of the premarket and postmarket setting. What we would like to accomplish by this model, to pull the data from the premarket clinical trial and observational studies in the postmarket setting, tapping into databases in the United States and outside of U.S. and published data, and apply simultaneously very statistical methodologies to give us better understanding and inform our decisions better in the future.

And this is my last slide. I would like to again let you know that we are launching an important initiative called MDEpiNet, which stands for MD, Medical Device Epidemiologic Network, and this is going to be a formal collaborative relationship with leading academic centers. We are having the public workshop on April 30th, this year. The *Federal Register* notice is going out this week, and we're going to be setting up the infrastructure that will be tasked to address all the gaps methodologically that exist in the evaluation of medical devices throughout the product life cycle.

Thank you very much for your attention, and I wish you a successful day. Thank you.

DR. HURST: Thank you, Dr. Marinac-Dabic.

We'll now proceed to the sponsor presentation for the Deep Brain Stimulation System.

I'd like to remind public observers at this meeting that while the meeting is open for public observation, public attendees may not participate except at the specific request of the Panel.

The sponsor will introduce the speakers. There will be a total of 90 minutes.

DR. GRAVES: Thank you, Dr. Hurst. Good morning, Panel members. My name is Nina Graves. I'm the Epilepsy Program Director at Medtronic. I'm a pharmacist by training, and I've a spent the last 30 years of my career working in the field of epilepsy, 20 years at the University of Minnesota, and for the past 11 years at Medtronic.

Though I'm standing before you, I must take a moment to thank the Medtronic team for their tireless efforts in preparing for this review. In addition, I want to recognize and thank both the FDA and the Panel for your time that went into reviewing the materials.

With the assistance of two of our SANTE investigators and a biostatistician who is an expert in GEE analysis from Duke University, we will be reviewing with you the study results over the next 90 minutes. This study investigated the safety and efficacy of deep brain stimulation for epilepsy.

Deep brain stimulation, or DBS, uses an implantable neurostimulator to deliver electrical stimulation to the chosen anatomic target. In the case of epilepsy, this target is the anterior nucleus of the thalamus or ANT. SANTE is the name of our trial. It is short for Stimulation of the Anterior Nuclear of the Thalamus for Epilepsy.

Prior to getting into the details of our results, I would want to take just a minute to provide you some context about DBS therapy.

DBS is currently FDA approved for four disease states. Since 1995, more than 75,000 patients have received DBS therapy. DBS therapy for epilepsy is a proposed new indication.

DBS was first approved in 1997 for central tremor. This was followed in 2002 for Parkinson's disease. Both of them were full PMA approvals. The two subsequent approvals, Dystonia and OCD, Obsessive Compulsive Disorder, were approved as humanitarian device exemptions similar to orphan drug status in 2003 and 2009.

This timeline somewhat parallels the timeline of DBS for epilepsy. The pilot studies of ANT DBS for epilepsy was initiated by physicians in the late 1990s. Those physicians shared their experience and data with Medtronic to enable an evaluation of the potential usefulness of the therapy. This also allowed us to work with them to develop the SANTE study protocol, the results of which we will present to you today.

The IDE was submitted in early 2003, after negotiations with the FDA, and approved at the end of that same year. The first patient was implanted in early 2004, and the last patient reached the one-year follow-up visit in June of 2008.

We met with the FDA prior to submitting our PMA in December of 2008 to discuss the safety and efficacy results as well as the handling of the data from the outlier subject, which we will be discussing today. We subsequently submitted our PMA in June of 2009.

As we go through the presentation this morning, we will discuss with you the devastating consequences of refractory epilepsy. In addition, we will show that DBS therapy is effective in this group of individuals with few, if any other, treatment options. Lastly, we will discuss the safety profile in light of the consequences of continued seizures in these individuals.

You have all received the briefing documents prepared by us as well as the FDA. In addition, you have received several questions from the FDA to help them in their evaluation of the efficacy and safety of this therapy.

The FDA's interpretation is that the trial did not meet its primary objective. However, the FDA has asked you to consider whether the primary analysis with the outlier patient removed provides a reasonable assurance of therapy effectiveness. Additionally, the FDA has also asked you to consider whether data from the final month of the blinded phase, month 3 to 4, also provides a reasonable assurance of effectiveness.

Just as you, we would like to ensure that the data is being fairly evaluated to determine the true effectiveness of the therapy. In our presentation this morning, we will show you that we have solid evidence that we have indeed passed the primary objective utilizing the alternative analysis. This alternative analysis removes the data from one patient.

Just as you, we are extremely reluctant to exclude pertinent data. However, we will demonstrate that if there is ever a reason to consider analysis with data excluded, this is the time. Indeed, the data from this subject and the alternative analysis meet the International Conference on Harmonization guidance on statistical principles for identification and handling of particular values leading to an outlier effect. We would like you to strongly consider this alternative analysis since we believe that the inclusion of this subject's data has truly obscured the primary analysis and the true value of this therapy.

In addition, the FDA has asked your opinion on whether long-term data should be considered along with the blinded phase results to establish efficacy. Given the chronic nature of refractory epilepsy and the long-term commitment made by patients who undergo device implantation, we strongly believe that long-term results are critical in establishing whether the therapy has lasting value.

Over our remaining time, we will provide you with a brief background on epilepsy, the SANTE study design, as well as the safety and effectiveness data from the study.

Dr. Robert Fisher will be presenting a great deal of this information. As most of you know, he is the Director of the Epilepsy Program at Stanford University as well as the overall study principal investigator for the entire SANTE site. He will start by providing a brief description of epilepsy. I'll then come back and provide you an overview of the SANTE study design and conduct, and Dr. Fisher will then provide an overview of the SANTE patient population.

Dr. James Rochon, a biostatistician from Duke University and an expert in GEE analysis, will then review the statistical approach that was prespecified in the protocol and describe the statistical modeling that was conducted. Since the interpretation of these results depend upon the understanding of the statistical as well as the clinical rationale for removing the outlier subject's data, Dr. Evan Sandok, the outlier subject's treating physician, will describe the events that occurred over the 48 hours that the subject first received stimulation.

Dr. Fisher will return to provide you with the remainder of the presentation.

We are also very fortunate to have several additional epilepsy experts that will help us answer some of your questions. We have two additional SANTE investigators, Dr. Doug Labar and Dr. Vicenta Salanova. They have both enrolled and continue to follow a large number of patients in the SANTE study at their sites.

Dr. Michael Kaplitt is one of our SANTE neurosurgeons from Cornell University who is also very experienced in DBS for other indications. Dr. Alexander Troster is a neuropsychologist from the University of North Carolina who has been consulting with us from the time of study design.

Finally, we have Joyce Cramer who is President of the Epilepsy Therapy Project and faculty at Yale University's School of Medicine, who is a quality of life in epilepsy expert.

Now I would like to introduce Dr. Robert Fisher, well known to many of you. Dr. Fisher is the Director of the Epilepsy Program at Stanford, the former President of American Epilepsy Society, former editor-in-chief of the *Journal of Epilepsia* and current editor-in-chief of the widely referenced website, epilepsy.com. He's the overall principal investigator for the SANTE trial. Dr. Fisher.

DR. FISHER: Thank you. Mr. Chair, Panel, thank you for the opportunity to address you.

I'm the overall PI. I had a key role in the design of the trial. I've done laboratory animal research in this area, and I'm a practicing neurologist and epilepsy specialist.

To avoid any conflict of interest, I've taken no money from Medtronic for the past decade, no speaker fees, no honoraria. They do pay my travel expenses to here and to rehearsal meetings, but I have no equities or other financial interests.

Many of you on the Panel are major experts on epilepsy already. So please forgive me for giving a brief background for those whose expertise may be in other areas.

Epilepsy is a brain disorder characterized by having at least one seizure together with an enduring predisposition to have other seizures. Manifestations can range from minor sensations to loss of consciousness to complex automatisms to motor behavior, and there are considerable other associated features. Epilepsy is not just seizures. Cognitive, psychological, and social consequences of a condition, including limits on driving, work, relationships, parenting, risk of injuries and deaths, and comorbidity such as depression and thinking impairment.

The International League Against Epilepsy categories seizures as those with partial onset distinct from those that are apparently generalized from the start. Seizures can be unclassified usually because of limited description.

Partial is a synonym for focal. With a simple partial seizure, there's no decreased consciousness, awareness, or memory, whereas with complex partial seizures, there is. A complex partial seizure therefore has greater seriousness and impact.

Any seizure that starts partially can secondarily generalize to a tonic-clonic convulsion conventionally called grand mal by the public, if the abnormal electrical activity spreads to the entire brain.

In yellow, we have highlighted the seizures that were prespecified for special analysis. We included a non-official but useful type of seizure at the bottom called the most severe seizure as noted by the subject. This was the seizure type picked by the subject prior to the baseline phase as being most bothersome to them. In some cases, it was a secondarily generalized tonic-clonic seizure and in others a particularly troubling variety of their complex partial seizures.

Epilepsy is one of the most prevalent serious neurological illnesses that is able to affect people across the entire age spectrum. There are about 2.3 million adults in the U.S. with epilepsy and an annual incidence of 150,000 new cases per year. The majority of these have partial-onset seizures, which is the focus of our clinical trial.

About one-third are considered refractory because seizures are not controlled by medications or because medications produce intolerable side effects. This is a substantially needy population.

There do, of course, exist treatments now for epilepsy. The most important are antiepileptic drugs. There is surgery for a few people who have a localized and safe-to-remove seizure focus. There's a ketogenic diet mostly used for some forms of pediatric epilepsy, and there is the only currently approved device for treating epilepsy, which is Vagus Nerve Stimulation. It is a helpful device, but many patients do not get adequate relief from that device.

For people who don't have effective therapy from something on this list and continue to have refractory seizures, there is a major impact on their life. In fact, you will hear from some of them today. For some, their life and their hopes are in shreds and, of course, they wish for the miracle to remove all of their seizures, but they will settle for something that helps. That is in our hands today.

I'm often asked why we chose the anterior nucleus of thalamus as our stimulation target. ANT is strategically located in a circuit that connects superior frontal cortex with mesial temporal cortex, both key areas involved in seizure disorders. In animal and human studies, stimulation of the anterior nucleus can evoke potentials in hippocampus, which is the most seizure-prone structure in the brain that's often involved in complex partial seizures. Stimulation of ANT can reduce synchrony in cortex and hippocampus, and it can increase certain markers of inhibition.

The anterior nucleus was an original target of the pioneering neurosurgeon, Irving Cooper, who identified benefit in patients with epilepsy, and subsequent to this work, there have been six pilot studies, one of them my own, that have shown benefit for stimulation at this site.

This is the circuit of Papez showing a circuitry involved in emotion, in memory, and in seizures, with hippocampal outflow through the fimbria fornix to the mammillary nucleus of hypothalamus, then to the anterior nucleus. There's also a direct connection not shown, from anterior nucleus to superior mesial front cortex cingulate and via cingulum bundle back to entorhinal cortex and hippocampus to complete the circuit. You can see that ANT is strategically in the circuit involving the most important structures for epilepsy.

I will now turn the podium back to Dr. Graves.

DR. GRAVES: I would like to remind you of the proposed indication for use outlined in your preview materials. It also very nicely describes the study population that was included in the SANTE study.

The DBS System for Epilepsy includes both implantable components as well as external components that interact with and control the implanted device. The implanted components consist of the lead, the extension, and the implanted neurostimulator.

The lead is implanted in the anatomic area of interest, and again for epilepsy, this is the anterior nucleus of the thalamus. Two leads are implanted, one in the right ANT and the other in the left ANT. Each lead is connected to an extension, which are tunneled subcutaneously down the side of the neck and attached to the neurostimulator which is placed in a subcutaneous pocket in the pectoral region.

Communication with the neurostimulator is done by the clinician with the clinician programmer and by the patient with the handheld patient programmer. The clinician programmer is able to set all the stimulation parameters non-invasively using telemetry.

The patient programmer enables the patient to assess the status of their device and turn the device on or off if clinically necessary. In addition, the unique Intercept, which is our brand name, patient programmer, has a seizure button which the patient can press in the event of a seizure. The command from this button will log the button press as well as restart the stimulation cycle if that feature is enabled by the clinician.

I'm going to spend some time explaining the SANTE study design because we will be talking about it for the remainder of this time. There are five phases to the study: baseline, operative, blinded, unblinded and long-term follow-up. During all phases of the study, the subjects continue to record seizures on a daily basis. During the baseline, operative, blinded and unblinded phases, subjects were seen monthly and antiepileptic medications were held constant. Rare changes to AEDs were recorded as protocol deviations.

At the beginning of the three-month baseline phase, patients sign the informed consent and were enrolled in the study. After implant, there was a one-month operative phase. During this time, the operative phase, none of the subjects received stimulation.

The three-month blinded phase began at time of randomization one month after implant. Subjects were randomized either to the active group with stimulation on or the control group with no stimulation.

At the end of the blinded phase, subjects entered the nine-month unblinded phase. At this point, the control group stimulation was initiated at parameters identical to the parameters the active group received during the blinded phase. No subjects or clinicians were unblinded as to the group assignment.

Please note that this phase is distinctly different from the long-term follow-up phase since during the unblinded phase, parameter changes were restricted and the protocol required AED to remain stable.

At the end of the unblinded phase, subjects entered the long-term follow-up phase. During this phase, stimulation parameters and AEDs could be changed based on physician discretion. Subjects are seen in the clinic at least every six months. Monthly phone calls were conducted to collect both seizure and safety data.

During the remainder of the presentation, please note that across the top of many slides, right along here, is a bar. This bar will represent the phase that the data on that particular slide is from.

This is a complete list of the objectives for the study. As you can see, the primary objective is based on a comparison of seizure rate in the active group compared to the control group. There were also a number of secondary objectives and additional study measures.

To assess safety, the study was designed to very carefully collect all adverse events to enable a characterization of these. The other safety objective was to characterize the incidence of sudden, unexplained death or SUDEP.

Adverse events were collected during all phases of the study and continue to be collected today. To enable an assessment of the therapy over time, most of the efficacy measures were also collected during the open label phases of the study.

I'll now turn it back to Dr. Fisher.

DR. FISHER: I'll now present the results of the study. I should add parenthetically that the report of the study is coming out next week in the *Journal of Epilepsy* at least in the online version, but there's nothing in that paper that you won't see here today.

These are the eligibility criteria. Patients were eligible to enter if they were ages 18 to 65, inclusive, and had six or more partial seizures per month, with or without secondary generalization. I'll highlight that point because it's more seizures than usually is required for a drug study and, in fact, our patients had a median baseline seizure frequency of 20, which is a lot.

I think you can skim over the rest of the list. I'll highlight that Vagus Nerve Stimulator could be used, but subjects had to be willing to turn it off for a month to make sure it wasn't helping and then have it swapped out at time of the surgery.

This is an eligibility list that's abbreviated. We don't, for example, indicate that every subject had to have prior video EEG monitoring capturing at least one seizure, and they couldn't have progressive severe disease. Suicide ideation was not an exclusion criteria, which may become relevant to later discussion.

The demographics slide here makes two general points. First, the population was severely refractory at the onset with 22 years of epilepsy and about 20 seizures per month. Most patients were taking multiple epilepsy medications. Almost half of them had inadequate benefit, 45 percent here, from previous Vagus Nerve Stimulation, and 25 percent had inadequate benefit from previous resective epilepsy surgery.

The second point on the slide is in the right column. There are no significant p-values here which indicates that the randomization worked and the demographics of the active and the control group were comparable.

Here is the flow of patients through the study. We had 157 enrolled, and we had 110 implanted, the difference mostly being failure to meet eligibility criteria such as seizure counts. Because of stimulator pocket infections, two subjects, and forgive me, being a clinician, sometimes I'll call them patients, two subjects skipped from the implantation directly to the long-term follow-up phase. So 108 entered the blinded phase.

We have data on 102 subjects stimulated for at least two years. This is a very good retention rate for this line of work. So far 57 have completed three years of stimulation. All will complete by this May, and 91 remain active in the study.

Discontinuations took place mostly in the baseline phase here for not having adequate numbers of seizures or having status epilepticus, other reasons, or because they changed their mind about the consent process.

There was one death during baseline, a sudden unexpected death in epilepsy which occurred before stimulation. There were no discontinuations in the blinded phase, and small numbers of discontinuations in the unblinded and long-term follow-up phases.

Note that 14 discontinuations total from year 1 forward include 8 who were greater than year 3. Data after three years has not been presented in any of your packet documents due to the relatively low number of patients who have reached that time point.

I, also on this somewhat busy slide, would like to draw your attention to this one here, which is the only patient prior to three years who withdrew from the trial due to lack of efficacy. Please remember that for later discussions. There was only one.

Let's talk first about the three-month blinded phase that began after the three-month baseline and the one-month postoperative phase. We chose a three-month blinded phase for clinical, ethical reasons, since even three months blinded means that you had three plus one plus three, which is seven months during which we had to keep medications constant. We expected there might be a time effect in this study and would have liked to have made a longer blinded phase, but we felt we were going to lose patients because of instability of drug regimens in this population. So we made our best compromise. As it turns out, three months was sufficient in our opinion to document efficacy.

This slide shows the median percentage reduction in monthly seizure frequency during the blinded phase compared to the baseline phase. Although it doesn't show it on the graph, there is at baseline a substantial range in baseline seizure frequencies from a low of 6 to a high of 604 seizures per month. That's a 100-fold variation.

Therefore, the percent improvement is the most clinically relevant to how each patient would do rather than an absolute count of seizures. By definition, all patients start at 0 percent change relative to baseline by randomization, which is here, which is also the time for turning on stimulation. Both groups had already improved to a median of 20 percent over baseline. This equates to a median drop of about 3.3 seizures per month.

This improvement after implantation has been noticed in pilot studies. Its mechanism is unknown. One of the pilot sites in Toronto has hypothesized that there might be a micro lesion effect of putting the electrodes in the thalamus themselves. We believe that this effect in the first month after implantation is part of the therapy and needs to be considered in the analysis.

Placebo effect or regression to the mean, since people tend not to enter a study like this when their seizures are doing well, are among other possibilities to explain benefit before turning on the stimulator.

Now, when the active group is turned on to 5 volts here, and the control group, unbeknownst to the subjects, is left at 0 volts, the active group continues to improve here in the solid green line, whereas the control group does not continue to improve. This difference is not due to micro lesion effect, to placebo effect or regression to the mean, but to something specific to stimulation.

Our protocol specified in advance that we should trace seizure frequencies by month and include an interaction factor and sequential monthly visits because we had an expectation that seizures could improve over time. This has been seen in other stimulations, but the last month of the blinded phase, which is here, median improvement in those receiving stimulation was 40 percent compared to about 15 percent in the control group. This degree of improvement is clinically meaningful in this refractory population, and it is greater than the median percent improvement for numerous drug trials that have resulted in licensing.

Why do I put more emphasis on the final month? It's because we expect improvement over time, and this is the final month of the blinded phase, not a randomly picked month during the blinded phase.

The FDA is asking you to consider median seizure counts versus percent change, with a difference between active and control of 2.5 seizures per month. I believe this is an incorrect interpretation of the clinical results. It ignores the initial 3.3 seizure per month drop, which is part of the therapy. If you add that back in, it's 5.8 median seizures per month. This statistic involves two people, one from the control group, one from the treatment group, subtracting their seizure frequencies, the median in each. We believe that all of the data should be considered. It ignores the time effect factor, which was significant in the model as you will hear, and mostly the variability among subjects is large with 100-fold ratio of initial seizures. So most clinically relevant is the ratio of improvement to baseline. That's how we design the protocol.

The chart that I'm showing here is primarily for clinicians such as myself, but the statistical analysis of the data, the p-value, depends upon a model called generalized estimating equations, which was the model required by the FDA. The GEE analysis does control for the baseline number of seizures, which was a highly significant factor. The median seizure count does not.

For discussion of that model and the essential statistics, I turn the podium over to our consulting statistician, Dr. James Rochon.

DR. ROCHON: Good morning. My name is Jim Rochon from Duke University. My disclosures are that my consulting fees and travel expenses have been paid by Medtronic, but otherwise, I have no financial interest in the company.

So as Dr. Fisher mentioned, the primary model that was described in the protocol is the generalized estimating equation model, or the GEE model for short. This goes back to a paper that was published by Liang and Zeger in the mid-'80s, and it was also built into PROC GENMOD in SAS in the mid to late '90s.

It's similar to the more familiar analysis of covariance model in the sense that it allows us to evaluate treatment effect, time effect, the so-called main effects, and also their interaction terms. We can, if we want to, include design factors in the model, and it allows us to introduce baseline covariance such as the baseline number seizures that Dr. Fisher was describing earlier.

But we feel it's actually more appropriate in this type of setting for the following reasons. First, it allows for longitudinal data from the same subject over time, and during the blinded phase of this study, the diary data were grouped into three intervals, with a visit at the end of that interval. It provides for a correlation structure among the set of repeated observations from the same individual, and we used the exchangeable model.

There was also some variability in the timing of the observations within individuals and across individuals. So it allows us to adjust for the variability in the lengths of the different visits using an offset in the model. All our estimates that are derived from the model are standardized to a month of 28 days, and perhaps most importantly, it provides for data that are not normally distributed, and in particular, the number of seizures tends to be skewed towards the higher values. So to address that, we used the natural log link together with the negative binomial distribution.

Now, the study was analyzed according to an analysis plan that was specified and approved by the FDA before the database was logged. The analysis plan required that certain variables be included in the model, and that includes, of course, the treatment effect, the log of the baseline number seizures, and also the offset to account for the variable number of days between the clinic visits. The baseline seizures were included because they account for much of the variability in the outcome, and that allows us to see treatment effects with greater precision.

There were other variables that were tested to be included in the model, and they were included in the model if the p-value is less than .1, and that included the center effect and the treatment by center interaction, the visit effect, the treatment by visit interaction, and then covariance including demographic variables, age and gender, as well as epilepsy variables that are shown here.

The final model that we derived from this analysis were the variables that were required by the model and those variables that were significant at less than 0.1. So again we see the final model had the treatment effect. It had the visit effect and the treatment by visit interaction. We had the covariance, age, and we had logged baseline numbers seizures and then the offset again to account for variability in the outcome measure.

So all primary objective p-values were derived from this GEE model, and following standardized procedures, standardized statistical practice, the estimated mean number seizures were derived from the GEE model, and these are sometimes called least squares means. They were, of course, with the log link derived on the natural log scale, and it's difficult to interpret differences on a log scale. So we converted them back to the original scale, but the consequence of this is that the treatment effect is not measured by difference. It is rather measured by a ratio. So the treatment effect will be portrayed as the ratio, the expected number of seizures in the active group to the control. Of course, the null hypothesis here is that the ratio is equal to one. There's no difference between the two treatment arms, but a value less than one will imply that the active intervention is more effective than the control.

Now, we performed inferential analyses in a number of different ways. The primary analysis that was specified in the protocol is individuals who provided at least 70 days of diary data during the blinded phase of the study, would be included in that analysis. So that was the primary analysis that we performed.

Now, secondly, we will discuss with you shortly a patient that we considered to be an outlier, and we've alluded to this on a couple of occasions. The results from this one individual are extremely unusual relative to the other patients that are in the analysis, but we will show you that there are good statistical reasons to be concerned about these data. We'll also demonstrate that there are very good, sound clinical reasons for considering these data to be idiosyncratic. We feel that the data from this patient should be distinguished from the other patients in the analysis, and I should mention that this patient is in the audience today and will be speaking during the public session. So we performed an alternative analysis with the outlier, Subject A, removed from the analysis, and we'll come back and talk a little bit more about that later.

There was also a second subject that has been discussed back and forth, so-called Subject B. This subject was thought at least initially to have unreliable data. We will also demonstrate that there is no good statistical rationale for removing this individual from the study, and also we'll demonstrate that there is no good clinical rationale for removing this individual from the study.

So the alternative analysis was Subject A removed we feel is a very important analysis and should be the one that is taken to heart by the Panel.

Finally, there was a third analysis, the intent-to-treat analysis, and under intent-to-treat principles, the patient needed to provide at least one day of the diary during the blinded phase to be included in this analysis, and it turned out there was only one additional subject who provided 66 of the 70 days. So, again, we performed this analysis with the outlier removed and this patient included in this analysis.

So this table shows the tests of significance from the GEE analysis for the different terms in the model. In our analysis plan, we said that an interaction term would be considered for inclusion if it's p-value was less than .10. So in this case, you can see that the treatment by visit interaction is significant at .069 and therefore satisfies our criterion because an interaction term makes it more difficult to interpret the results from the study but it doesn't make it impossible.

At a fundamental level, it means that the treatment effect is not consistent from one time point to another, and this can arise for a number of different reasons. It could be that the treatment effect is smaller at the beginning of the study but becomes progressively larger as the intervention accrues over the course of the time domain. But the bottom line, I think, is that when you do have a significant treatment by a visit interaction, you're not really at liberty to interpret the treatment main effect. The treatment main effect asks is there a consistent difference between the two treatment arms and, of course, the interaction term says that it's not consistent over the time domain. So we need to look at the individual visits to determine how this interaction is manifested.

So you remember that the treatment effect is represented as the ratio between the expected number of seizures in the active group to the control, and that's what we're presenting here. These are the ratios over the time domain in the study. We have a dotted line here at the value 1. This is for the null hypothesis, that there's no difference between the two treatment arms. The difference here at the beginning of the blinded phase of the study is 1.20, but you can see that the confidence interval here includes the null hypothesis 1. So that's not statistically significant.

The value at the end of the second interval is actually 0.9, suggesting that there were fewer seizures in the active group compared to the control group, but again this interval includes the null hypothesis 1, so it's not statistically significant, but by the end of the study, there was a reduction. There were fewer seizures in the active group compared to the control. The estimate is 0.71, and the confidence interval is completely below the null hypothesis 1. So that would imply that there was a significant effect, at least in this analysis, in the primary analysis, by the end of the blinded phase of the study.

Now, let me also draw your attention to a couple of things. This actually shows very nicely how the interaction was manifested over the time domain of the study. The treatment effect was not significant at the beginning and then became larger and larger as we went through the study.

The other thing I want to draw your attention to is this very large confidence interval attached to the first time point. It's completely out of proportion to the other confidence intervals in the study. So it bears investigation to understand how this large confidence interval arose.

Now, again there's one patient we consider to be an outlier, and the GEE model provides different plots for identifying and investigating outliers. Here are two of these plots. The horizontal access here is just the patient ID, the different patients who were in the study, and then these are two statistics that arise out of the GEE model.

So basically what we're looking for is the kind of random variability of these points over the different subjects in the study, and for the most part, that's exactly what we see here.

There was one subject, number 40, down here in this plot, who sticks out a little bit here and also a little bit here but is employing no statistical rationale for removing this individual from the study. There needs to be some variability across the patients who are in the study.

There is also again Patient B, the patient that we think initially had unreliable data. That's not ID Number 40, and if you look at these points, you can't identify, I can't identify another individual who sticks out clearly, except with one exception, of course, who should be removed from the analysis. In fact, Patient B is somewhere in here, number 46. I don't see any obvious marker for him, and I don't see any obvious marker for Patient B in this plot either that would prompt me to remove this individual from this study.

The red dots also show individuals who had an increase in their seizures during the blinded phase as compared with baseline, and again I don't think any of those red dots stick out in a substantial way relative to the other patients in the study. So I would see no statistical rationale for removing these individuals from the analysis as well.

Now, in my statistical practice, I tend to be very cautious and very conservative about removing patients from the analysis, and in general, the FDA strongly discourages removing randomized patients from the analysis. The ITT analysis, the intent-to-treat analysis, actually prohibits this all together, and there's good reasons for this. It's much too easy to sort of cherry-pick the patients and to decide who should come in and who should come out and, in fact, slant the analysis in one way or another. So that's not what we're talking about here.

What you can see up here at the very top of this plot is subject A, our outlier subject who is clearly head and shoulders away from the other subjects in the analysis. We would say that this individual is qualitatively different from the other patients who are in this analysis and should be distinguished from them as we go forward.

So let me turn now to Dr. Sandok to give you the clinical details surrounding this case.

DR. SANDOK: Thank you, Mr. Chairman, Panel. My name is

Dr. Evan Sandok. I'm an epileptologist from the Marshfield Clinic. I'm also a SANTE principal investigator. My travel expenses have been compensated by Medtronic, and I'm a consultant for Medtronic.

This graph clearly shows the seizure frequency over time in the individual we refer to as the outlier subject. The spike in seizure frequency at the start of the blinded phase is quite clear. I'll now provide the clinical context for this case.

The outlier, as we referred to him, is a 43-year-old individual with a near lifelong history of seizures, since an episode of encephalitis as a small child. He's tried numerous medications and, in spite of these, has continued to have simple and complex partial seizures with secondary generalization. He lives in rural northern Wisconsin, three hours from my center. I met him just over 10 years ago when we did the initial evaluation to exclude him for epilepsy surgery. I've continued to treat him since.

He enrolled in the SANTE trial and underwent DBS implant procedure. At randomization visit, an unblinded programmer activated the Medtronic DBS device according to the randomization assignment. That same day, the patient had onset of a new type of seizure. He did not recognize the events of seizures until the next day, though he did recognize this as a new event and recorded them in his diary. The events were much shorter and milder than his previous seizures and were not recognized as seizures again. The events lasted a few seconds and had a frequency consistent with the known cycling of the device, every six minutes. One minute on, five minutes off is the current cycling.

I remained a blinded investigator, but based on his description the next day by phone, I felt that these events were most likely acute symptomatic seizures triggered by the device and not his spontaneous seizures. I suggested that he turn the device off with his handheld programmer to verify that these were, in fact, were acute symptomatic seizures and not the patient's typical spontaneous seizures which were the focus of this treatment. Upon turning off the device, the acute symptomatic seizures stopped.

The next day the patient was asked to turn his device back on during his three hour drive back to our office to see if the events reoccurred. He once again described acute symptomatic seizures triggered by the device which were short and mild. Upon arrival in my office, an unblinded programmer reduced the voltage set from five to four, and the seizures once again stopped, verifying again that these events were acute symptomatic seizures triggered by the device, not spontaneous seizures, and were voltage dependent. And EEG was not done to verify these procedures as the events were resolved with reprogramming.

This event was transient, and this type of seizure was never seen again, even when the same settings were used later in the study. We were unable to replicate this phenomenon later with a rechallenge. We increased the voltage as high as nine volts.

Here's a summary of the clinical rationale to remove the outlier. I'll not review these again. These were unique events not reflective of spontaneous epileptic seizures that are the focus of this therapy. Subject A is outlier for clinical and statistical reasons.

The FDA has described a second subject to consider for exclusion. We could have been clearer in the PMA and panel pack about the clinical aspects and timing in the subject. Though I'm not the treating clinician of the subject, I will outline the details for you.

Subject B met all inclusion criteria and no exclusion criteria. At month 3, during the blinded phase, the site informed Medtronic of a caregiver change. Training of the new caregiver was completed as per protocol. At month 9, 5 months later in the unblinded phase, a new seizure event which was psychogenic was reported. The site suggested that the subject diary may be unreliable.

Subsequent review of the blinded phase data around the time of the caregiver change demonstrates consistent seizure counts of the patient's nocturnal seizures for month 2 to 3 and 3 to 4 of 23 and 29, respectively. During blinded phase, only the subject's usual nocturnal seizures occurred. Psychogenic seizures do not occur during sleep.

Among many suggested sensitivity analyses, removal of the patient was tested. However, clinical review indicates reliable data during the blinded phase. There is no clinical or statistical reason to remove Subject B.

Dr. Rochon will now continue to discuss the statistical analysis.

DR. ROCHON: Thank you. Jim Rochon from Duke University.

Now, we conducted the analysis from the study according to ICH Guidelines and Section 5.3 of ICH Guideline E9 actually anticipates that there can be outliers in clinical research, and it describes a mechanism for managing an outlier and dealing and describing how to address an outlier.

So here we've actually quoted from these guidelines directly.

"Clear identification of a particular value as an outlier is most convincing when justified medically as well as statistically." And I would say that we have provided a very strong statistical and clinical rationale for considering Subject A as an outlier in this study.

"If no procedure for dealing with the outliers was foreseen in the trial protocol, one analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect should be performed and differences between their results discussed." So, in fact, this is what indeed we have done in this study.

So this again is the test of significance from the GEE model, but this time from the alternative analysis. This is the analysis to remove the outlier. The interaction term is now significant at .096, and if we follow the FDA's note in their Executive Summary and use .05 as the level of significance, then this is no longer statistically significant and we can interpret the treatment main effect here. The treatment effect p-value is .04.

So a main effect indicates that there was a consistent difference between the active intervention and the control but over the course of the blinded study. So on average over the blinded study, there was a significant difference between active and control. But note that this does not necessarily mean that there's a difference in every single time point. It means that on average over the blinded phase, there was a significant difference between the two treatment arms.

So here again is our plot that shows the ratios of the active to control over the course of the blinded phase of the study. Here's a null hypothesis value 1 once again. The light blue lines correspond to the original analysis, the primary analysis. Now, the dark blue lines correspond to the alternative analysis, and you can see very clearly that all the point estimates at the different time points are all now below the value of 1.0. It's significantly below the value of 1.0 at the end of the blinded phase. This point estimate is 0.71, which suggests that there was a 29 percent reduction in the number of seizures in the active group compared to the control group and is significant at .002.

Finally, we also performed the intent-to-treat analysis that I had mentioned before. This added one additional subject to the analysis, a individual who provided I believe 66 out of the 70 days towards the analysis. We again removed outlier Subject A from this analysis, and we basically see the same results. The treatment effect is significant at .038, in this case again suggesting that there was a significant benefit for the active intervention compared to the control over the course of the blinded phase of the study.

This is a plot again of the ratios over time. Again, the ITT analysis is the triangles and the dark blue lines here, and it basically shows the same pattern. The point estimates are all below the null hypothesis value 1, significantly so, by the end of the blinded phase of the study.

Now, there are a number of sensitivity analyses, and I'm not going to go into in great detail in the presentation. They were provided in the materials that we provided to you, a per-protocol analysis and as-treated analysis. We did perform due diligence and remove Subject B from the analysis, but the results clearly indicate that without the outlier, virtually all were statistically significant over the entire blinded phase of the study. So removing outlier Subject A, we had a significant treatment main effect, and regardless of whether the outlier was in or out of the analysis, we had a significant result by the end of the blinded phase of the study with p-values less than .006.

So to summarize the primary analyses, the protocol-specified analysis was heavily influenced by an outlier, and I provided the statistical rationale, Dr. Sandok provided the clinical rationale for characterizing this patient as an outlier and why we believe that his data should be distinguished from the other patients in the analysis.

We followed published ICH Guidelines on how to address an outlier in the analysis. We compared the two results, and when we removed the outlier, there was a significant treatment main effect indicating that there was a significant benefit for the active intervention to the control over the entire blinded phase of the study. The ITT analysis also produced the same effect, and all three analyses demonstrated that there was a significant benefit by the end of the blinded phase of the study. So this table demonstrates and summarizes all the analyses that we performed on the primary outcome measure.

DR. FISHER: I'm not a statistician, but I learned a lot of statistics from this trial. I'm a clinician. So let me just go off script for a moment and tell you, as a clinician, what I just heard.

We had one patient who had seizures every six minutes in the two days that we turned on the stimulator. That produced 210 acute symptomatic seizures from the stimulation. When you include those 210 seizures in the primary analysis, since the patient was in the stimulated group, there's no longer overall significance for the p-value according to the model, although there still is for months 3 to 4, which is one of the time-related considerations we prospectively looked at.

But why in the world would you include 210 seizures triggered every 6 minutes, which immediately went away when turning the voltage from 5 to 4 volts, in with the spontaneous seizures that we're trying to treat with this protocol? As a clinician, that doesn't make sense to me, and with that outlier Subject A removed, there is clear statistical significance of stimulation over control in the blinded phase of the trial according to the protocol as we proposed it and FDA approved it.

Since I believe that we did meet our primary study objective, it's legitimate to look at certain subgroups that may show significance. We didn't power the study to look at seizure type per group, but complex partial seizures shown here did turn out to be specifically improved over control as a subtype provided that we separately isolate the complex partial seizures of the outlier.

Secondarily generalized seizures also improved but with small numbers, and they really are small on the slide, 19 and 21, and variability, it did not come close to statistical significance. The most severe seizure type did improve. For 57 percent of the subjects, this was a secondarily generalized seizure.

Now, the FDA has included in their material to you an analysis that was not protocol prespecified using a worse case interpretation, by which I mean that our protocol specified that if subjects didn't have seizures in the baseline phase, you couldn't use that as a denominator for a ratio of improvement. So we were not going to count them in the worst case analysis, whereas the FDA did include this division by zero case in their packet.

Not shown is efficacy by lobe of seizure origin. It was better in the active group for temporal lobe origin but not for other lobes. Again, the study wasn't powered for this particular subgroup analysis, and it's quite possible that other groups would have shown efficacy had there been larger numbers. Since we can't speculate on this accurately, we believe that the existing study entry criteria ought to govern the indication, which is partial seizures with or without secondary generalization.

I mentioned that about half of the trial had the Vagus Nerve Stimulator removed because of an adequate benefit and about one quarter were not helped by prior resective surgery. Those patients had about the same degree of benefit from stimulation in the blinded phase as did others in the trial.

Now, refractory seizures can cause injuries. In the initial PMA, we included only injuries that met the MedDRA terms, which are injury, contusion, and excoriation. However, this slide, which was included in your packet of information, is updated with all seizure-related injuries. For example, also including sprain, laceration, hematoma, and others.

Those patients in the actively stimulated group had significantly fewer injuries, 7 percent, compared to 25 percent in the control group. That has a p-value of .01. The FDA is asking you to consider whether this results from an increase in the control group injuries. It does not. The baseline injury frequency for the active group, not shown on this slide, was 20 percent versus the 7 percent, and that value had p=.05. The baseline injury frequency for the control group was 16 percent versus this 25 percent with p=.24. The same significance pattern holds if we restrict to the original MedDRA terms only. So this is a real finding and a gratifying one.

The protocol agreed to look at a number of secondary objectives and additional study measures. Among these, only the reduction in most severe seizure type was significant during the blinded phase. Highlighted in yellow is the group that is favored, and the trend can be seen to favor active stimulation for most of the measures but not with statistical significance. I won't take time to read these one by one. They're in your handout.

So here is the summary of the blinded phase efficacy results. We saw a statistically significant reduction in the rate of seizures compared to baseline for the active group compared to the control group. A 40 percent reduction by the end of the blinded phase is clinically meaningful in this population.

We showed value for three measures of severity. Complex partial seizures improved with stimulation as opposed to the simple partial seizure. The seizure type designated most severe, prospectively by the subject, improved, and seizure-related injuries were significantly less in the stimulated group. All analyses found a significant benefit for stimulation in the final month of the blinded phase. In the FDA's words, these results provide reasonable assurance of effectiveness relative to baseline.

Let's move on now to the nine months of the unblinded phase. During this segment, we continued to collect data from all of the subjects and to keep medication as constant as possible. In fact, only two subjects added an additional AED during this time. This is not your typical cherry-picked group of only the people who stayed in a trial because they were doing well.

Here we have a graph of the median seizure frequency percent change, in other words, change relative to baseline by groups summarized by month. This first part of the graph, you've already seen. Now, we're showing you, as Paul Harvey would say, "the rest of the story."

This analysis includes those subjects with at least 70 days of diary in each 3 month interval. At the second yellow arrow here, we turn the control group subjects from 0 volts to 5 volts. We left the active group at 5 volts. Neither group was told what the initial settings were. So they don't know whether they were changed.

Those patients in the control group began to improve at a rate over the next three months, if you were to draw a slope, from here to here, and here to here, three month slopes, at about the same rate that the active group started to improve three months earlier when their stimulator was turned on. Patients in the active group, on the other hand, don't show any change. This is reassuring in terms of seeing a real effect due to stimulation.

We believe that the unblinded phase has importance because an invasive therapy such as DBS, if it had only short-term benefit, it would be of limited clinical value. We need to see that benefit is sustained. Long-term study also provides additional safety information.

As you can see, efficacy improved over time with a 41 percent median seizure reduction at one year of stimulation, 56 percent improvement at two years, and 68 percent for those 42 patients who have so far completed three years of stimulation. This is one-third their baseline seizure frequency.

By the way, we put n's at the bottom, and you will see what seems to be differing n's in different analyses. This is because efficacy analysis requires at least 70 completed diary days in the 3 months prior to the visit whereas safety and adverse event data do not.

FDA has commented that 19 patients dropped out from the long-term data. Only 11 of these were in the dataset before year 3. Again, we're not cherry-picking the good responding to following long-term. The usual method of handling such dropouts is by intent-to-treat analysis using last observation carried forward.

The first blue bar here, 41 and 56 percent, is the one that you saw in the previous slide for at least 70 diary days. We analyze by several methods, all of which produce similar results. I draw your attention to the third striped bar, which is the intent-to-treat analysis with last observation carried forward to account for patient dropouts. It is essentially identical to the blue bars.

The worst-case analysis, which is this last one on the right, at one year and at two years, was suggested by the FDA, and I'm obliged to tell you that it is shown here for the first time. What it means is that if there were missing data, we used the worst-case assumption of 100 percent worsening. It also does not show substantially different results.

Now, at time of data lock, 81 patients had passed the two year stimulation mark and had at least 70 days of diary entry. How well they did individually is shown on this slide. This chart has one vertical bar depicting their seizure frequency for each of the 81 subjects at the last three months prior to reaching two years of stimulation. Up means more seizures and down means fewer seizures. Now, you can have any multiple of baseline seizure frequency, but you can only improve 100 percent, which accounts for the vertical asymmetry of the graph.

For the three subjects on the left, in this box, there was greater than a 50 percent seizure increase. The increases in these three patients shown in the chart at the bottom were due to simple partial seizures. As shown in the right column, the numbers are small, complex partial seizures improved 66 percent in one patient, 1 percent in another, and 100 percent in a third. So these are simple partial seizure increases.

Second, there were 6 patients to the right of this slide who are 100 percent improved, which is seizure free.

Now, the next slide shows more details on seizure freedom. A total of 14 subjects were seizure free for at least 6 months, an interval we highlight because, for example, it will get you a driver's license in most states.

Anyone above this halfway point, between zero and one year, is six months seizure free. There are two bars for some because some relapsed, then became six months seizure free again.

Six subjects were still seizure free at the end of the data cutoff, and eight subjects were seizure free for one year or more. Since you couldn't be seizure free for even as long as a month in the baseline, this is pretty impressive.

After one year, physicians could change epilepsy drugs. Here is the seizure frequency information at two years grouped by whether antiepileptic drugs were altered with no change, increased drugs, decreased drugs, and both. Median seizure frequency improved for all subgroups. It's not surprising that the no change group had the biggest improvement because when patients are doing well, we tend to leave their drugs alone.

Again, I emphasize that, of course, during the blinded three months, and the baseline, and the operative phase, but also the nine months of unblinded, we kept the drugs constant whenever possible, and only two patients had new antiepileptic drugs added during that time.

So responder rate. The responder rate is the percentage of the group whose seizures were cut in half or better during the blinded phase. The degree of improvement in most patients was usually less than 50 percent, and we didn't see a difference in responder rates.

As we extend into the unblinded and long-term follow-up phase, we measure responder rates of 43 percent, 54 percent, 67 percent for years 1, 2, and 3. We can talk about this more later if you want.

Quality of life in epilepsy was assessed by a 31 question questionnaire. It's not a tool for measuring short-term change because 12 of the answers wouldn't change within 3 months. There was no change in quality scores during the three month blinded phase. In the long-term phase, there were the improvements that you see. Our consultant, Joyce Cramer, and the literature tell us that improvements of five or more are clinically meaningful.

The FDA asked us to ask patients how satisfied they were with the therapy. 74 percent reported being satisfied or greatly satisfied, 81 percent said they would do it again, and 88 percent would recommend it to a friend, presumably one who had something that needed the brain stimulation, not all their friends.

So here's the efficacy summary conjoined for blinded and unblinded stage. As you saw earlier, the seizure rate was reduced in the blinded phase compared to control with a 40 percent median decrease and a reduction of complex partial seizures, most severe seizures, and injuries linked to seizures. We now add that efficacy is maintained in the long term such that by three years of stimulation, seizures are reduced by 68 percent, in other words, to 1/3 of their baseline level.

The quality of life scores and responder rates improve long term; 13 percent of subjects were seizure free for at least 6 months, some for several years. Therefore, DBS is efficacious in this patient population.

Let's move on now to the other side of the coin. Our safety objectives were to characterize adverse events and to track sudden unexpected death in epilepsy, abbreviated SUDEP. Adverse events were captured based on subject report, neurological and physical exam, and findings on neuroimaging.

Events were categorized by seriousness, severity, and whether they were believed to be caused by the device. Please recall that seriousness is not the same as severity. Serious reactions are those that result in death, permanent impairment, hospitalization, prolongation of hospitalization, and so on. Severity is characterized by the patient's local investigator as being mild, moderate, or severe. All adverse events were translated into standard terms and adjudicated by the Clinical Events Committee and reviewed by the Data Safety Monitoring Board.

As with drug studies, every adverse event was collected, including sore throats, colds, flu, et cetera. Therefore, the absolute number of adverse events can appear quite high for the multiyear determination of the trial.

There were two adverse events that were significant in the blinded phase. So allow me to highlight them. They are depression and memory impairment. Depression is a common comorbidity in refractory epilepsy populations that occurs at a rate approximately four times greater than for the general population in at least 20 percent of the people with refractory epilepsy. Depression, even severe, was not an exclusion criteria for the SANTE study although history of psychiatric hospitalization for suicide attempts were.

As we'll see in the subsequent slide, measured profile mood scores did not differ in the blinded phase by treatment group. However, nine patients reported individually adverse events that can map to the term depression. Prior history of depression existed in seven of the eight, and three were on antidepressant medication at baseline. If they had reported worsening, this was counted as a depression adverse event.

Now, since eight of the patients reporting depression or worsening were in the active group, and only one in the control group, this was statistically significant. One of the events was serious. Eight were not. None were severe. The depression resolved in half the subjects. Measured depression scores were unchanged or improved in five of the eight subjects.

For those of you clinicians who are aware of the phenomenon of forced normalization by which depression occurs as seizure improves, four of the patients had a greater than 50 percent improvement in seizures by the end of the baseline.

In the unblinded and long-term follow-up phase, reports of depression decreased as you can see here in these numbers. None was serious, 23 were mild or moderate, and 1 was severe. Objective testing showed no change or improvement in 80 percent.

Because of this data on depression, Medtronic has included information about depression monitoring in their proposed labeling which is in your packet and which you can read.

In the baseline phase, one patient reported suicidal ideation, and another made a suicide attempt. Both were discontinued from the trial. Suicidal ideation occurred in one or two patients per year during the trial. Sadly, suicide ideation events are part of the natural history of epilepsy and considering that we saw two in the three month baseline and in the stimulated patients the lower rate of one or two per year.

One patient made a suicide attempt after year three and one patient actually committed suicide. More about him in a moment.

The patient who did commit suicide was a 29-year-old man who had preexisting depression. He had been on venlafaxine, which is Effexor, for several years prior to entering the trial. He was seen in the clinic three days prior to his suicide with no indication of any change in his existing condition. He was at the time 3.5 years into stimulation. However, his stimulation battery had run down a few weeks before and he was awaiting replacement. The battery had uneventfully run down twice before. He had longstanding depression. He recently had been divorced. The investigator, the Clinical

Events Committee, and the DSMB did not believe the suicide was related to DBS therapy or to any rebound effect of stopping stimulation.

Because this happened when he had been off stimulation, we looked to see if stimulation withdrawal might be a risk factor for suicidal events and reviewed data on 12 subjects with stimulation off for at least a month. None resulted in suicidal ideation or acts.

Another adverse event seen in the blinded phase was memory impairments. Again measured neurological psychological test values did not show group differences, but individual subjects reported adverse events related to memory, more were in the stimulated group, resulting in a significant difference. None were either serious or severe and all the memory problems resolved.

Long term, there were a few additional individuals who reported memory problems. You see the numbers here, 1.9, 1.0, 8.8 percent. Over half the subjects reporting had unchanged or improved memory scores at their next evaluation after reporting the adverse event.

The FDA and trial designers, us, wanted objective measurement of neuropsychological and depression scores at baseline, during the blinded, unblinded, and long-term phases. To make a long story short, none was significant.

The FDA also will present data on reports of anxiety and confusion in the blinded phase. These events did occur more often in active subjects, but the differences were not statistically significant.

In addition, when the control subjects were turned on, there were no anxiety or confusion adverse events in the first three months, except as related to one patient who had non-convulsive seizures with stimulation. More about him in a minute.

Seizure counts. So seizures were, of course, efficacy measures, but we also reviewed them for safety purposes. Ten patients in the stimulated group and sixteen in the control group showed an increase in seizures during the blinded phase. The striped red bars are control patient percentage change from baseline, and the solid green bars are the stimulated patients. The red bars are bigger, control patients.

Except for the outlier with seizures stimulated by the cycling of the stimulator, shown here on the left, all increases in the active group were less than 50 percent. In contrast, three subjects in the control group had increases between 50 and 115 percent. Some of these increases overall are rather small such as two percent. Clinicians recognize that seizure frequencies fluctuate up and down even in an improving group of patients.

Seizures would be reported as an adverse event if there was a new seizure subtype or if the seizures resulted in hospitalization, an ER visit, or status. Investigators could also submit any event at their discretion.

In the blinded phase, there were no statistically significant difference in seizure adverse events, and there were no new generalized seizures. Local investigators believe that some seizure events were due to medication noncompliance or low serum levels. Occasionally a seizure would occur in public, and the subject would be taken to an emergency room.

Let's look at seizure adverse events that occurred in the first week of stimulation. One again was with the outlier, this one, who has been discussed in detail. Another, which is this third patient down here, confusion, status epilepticus, was a patient who reported confusion when his stimulator was turned on. He was in the control group. So when it was turned on at the beginning of the unblinded phase, up to 5 volts, he developed confusion, and a few days later his EEG showed a picture consistent with non-convulsive seizures. Even status, even though his only symptom was confusion.

Three other subjects had simple partial seizures, one longer than usual, one a new simple partial type, and one a prolonged aura. Most of these occurred on the first day of stimulation and resolved with reprogramming or sometimes no intervention.

I mentioned status. Status occurred in five patients during the trial. However, three of the five were not receiving stimulation when they had status. Two of them were in the operative phase, believed by the investigator to be related to missing antiepileptic drugs around the surgical procedure. Four of the five were non-convulsive, and all five recovered uneventfully.

Medtronic proposed labeling, you can scan over it. It recommends warning the patient of acute seizures when first turning on the stimulator and being prepared to lower the voltage if this occurs.

Now, the most frequent serious adverse event was missing target in the anterior nucleus of thalamus, and it was classified as serious because then you had another operation which prolonged or caused an additional hospitalization. Overall, 9 of 110 subjects required lead repositioning. That rate was cut in half in the second half of the trial. There is a learning curve. All of the patients were successfully repositioned.

The next most common serious adverse event was an implant site infection in 8 out of 110 subjects, which is a rate of 7.3, similar to that of other DBS therapies. None of the infections were brain infections. Five required removal of hardware. Two chose to have it reimplanted.

Five people died during the study. None of the deaths were considered to be related to the device implantation or stimulation. Every death had to be evaluated for SUDEP. Three deaths are listed as being SUDEP related. SUDEP is probably cardiac arrhythmia or respiratory arrest, but the exact pathophysiology is unknown and still debated.

The prespecified procedure in the protocol for counting SUDEP was to include definite or probable cases in patients who received stimulation. For completeness, we also calculated a third case of possible SUDEP, this one, but this was a woman who drowned in a bathtub.

The top row shows an instance of probable SUDEP before DBS implantation, and that is not included in the SUDEP rate. One additional death has occurred since database cutoff, after a prolonged ICU stay, but we do not have the details or the review of that case yet.

The calculated SUDEP rate in this trial is 5 per 1,000 patient years, which is lower than the published SUDEP rate for the population of 9.3 in surgical referral groups. Even if we were to include the possible case of SUDEP, the drowning in the bathtub, the rate would still be lower at 7.6.

Now, your FDA document mentions 9.2 deaths per 1,000 for SUDEP. To get this number, I believe they have to include the bathtub drowning and they have to ignore the pilot studies, both of which are contrary to the prospective protocol agreement because we were asked to include the pilot data in the SUDEP calculation and those years do go into the calculation.

Intracranial hemorrhage is a known potential complication of DBS therapy for movement disorders. Let me make up some time by saying we had no symptomatic hemorrhages. The hemorrhages are only because we did MRIs on everybody after the study, and in four cases, we had small amounts of bleeding. We have the MRIs here if anyone wants to see them.

In one case, the patient fell, hit their head, and bled into an existing poor encephalic cyst. None of these patients would have known they had hemorrhages if we hadn't done the imaging.

In the study were 49 patients who received a MRI with abandon, which is to say clipped VNS leads. There were no reported adverse events from this. The labeling that Medtronic proposes is the most conservative of the approved standards for either DBS or VNS.

So here's the safety summary. First, we didn't have any unanticipated, serious, device-related adverse events at any point in the study. Depression and memory impairment were reported more frequently in the active group. Depression monitoring is therefore addressed in the proposed labeling. The actual measured numbers for psychological and cognitive data didn't show any group differences.

Patients can have acute symptomatic seizures upon initiation of stimulation, which can be addressed by watching them and lowering the stimulation voltage. That is discussed in the proposed labeling.

There were no device-related deaths and no symptomatic hemorrhages. The SUDEP rate was no higher than expected for this refractory population.

In general, procedural and hardware-related risks are consistent with those experienced in other DBS therapies, and I will now turn the podium back to Nina Graves.

DR. GRAVES: Thank you, Bob. I'm now going to review three separate topics with you, clinician training to assure appropriate utilization of the therapy, our proposed post-approval studies, and some specific sections from our labeling.

Since DBS is an approved therapy for other indications, we have existing training programs in place already. These programs will form the basis for the new training that we will provide specific to epilepsy. We will utilize our current medical education curriculum for existing DBS therapies as that baseline for clinician training for Medtronic DBS for epilepsy. The existing infrastructure will be enhanced to include neurologists, epileptologists, neurosurgeons, and other key individuals involved in the care of epilepsy patients.

Some examples of the training programs we have are listed on the slide. First, we have a group of highly skilled field technical support personnel. These individuals will conduct center evaluations and may provide on-site training of the neurosurgeons.

In addition to field-based support, we will also develop courses for any healthcare clinicians who will utilize the therapy. These will be delivered live as well as through web-based training. It is expected that the training program will be reviewed and revised in scope based on continuing experience with the therapy and feedback on training needs from clinicians.

In our information provided to you in the briefing materials, we have outlined a plan for post-approval studies. We believe that we have established the safety and efficacy of DBS therapy for epilepsy through the SANTE randomized control trial and through extensive clinical and commercial experience with other DBS therapies.

To augment the safety and efficacy data already collected, Medtronic has identified the three objectives shown on this slide. Medtronic provided an outline of its objective for the post-approval phase which was intended as a baseline for discussion to determine a suitable study design. We look forward to hearing the Panel's opinion and working with the FDA after this meeting to finalize our post-approval plans.

We would like to point out that our proposed labeling has some warnings and precautions related to some of the information that the FDA has asked you to consider. We have already shown you the proposed label related to warnings on depression and seizures upon initiation of stimulation. In addition, we have precautions related to interactions between DBS and other implanted devices and the possibility of prolonged time to therapeutic effect.

The next few slides outline the exact wording of the proposed labeling. We've included these for you as a reference and will not discuss them in detail.

At this point, I want to bring back Dr. Fisher so he can discuss his views on the overall risk/benefit therapy of this device.

DR. FISHER: These are the overall conclusions. Refractory epilepsy is common, and new therapies are desperately needed.

DBS showed benefit in individuals who are having many monthly seizures, not responsive to multiple medications, and often inadequate benefit to prior VNS therapy or epilepsy surgery. Thalamic stimulation was proven effective in this double-blind trial for partial and secondarily generalized seizures as the entry criteria provided that we eliminate seizure counts from stimulation-triggered seizures in one patient immediately after the onset of therapy.

Those acute symptomatic seizures should not be averaged with counts of spontaneous seizures because they are a different type of seizure from those we are trying to treat, and they are manageable by observing the patient and turning down the dial.

Even if you do choose to count these stimulation-triggered seizures, although I don't know why you would, the benefit of stimulation is evident at the final month of the blinded phase, a time effect that we anticipated and built into the model.

The 40 percent median improvement at the end of the blinded phase was substantial in this patient population. It's greater than is seen in many prior clinical trials leading to licensing, and it is done with a more refractory population at the start.

In addition to reducing seizure numbers, we also ameliorated important markers of seizure severity. During the blinded phase, we reduced the numbers of complex partial seizures, the seizures considered most severe by the patient, which were usually secondarily generalized seizures, and injuries produced by seizures, all statistically more than in the control group.

Beneficial effect of stimulation was lasting. We did not see the familiar and transient honeymoon effect of adding medication after medication to the regimens of these refractory patients. By three years of stimulation, seizures were at a median 68 percent improvement relative to baseline, that is to say a third of their initial level.

The safety profile was, I think, acceptable. Compared to epilepsy surgery, this does not require removal of tissue, and DBS is both adjustable and reversible. Compared to the devastating social, psychological, and health effects of uncontrolled epilepsy, the risks are reasonable.

I'm the principal investigator of the trial, but I don't work for Medtronic. I work for about 1,000 patients in my clinic who have refractory epilepsy. DBS is not a minor addition to our therapeutic options. It is a new type of treatment. It's at the beginning, but I think it already shows efficacy and great promise, and I would ask the Panel to look at all of the data with wisdom and compassion and recommend approval for an appropriate group of patients with severe and uncontrolled seizures, not for all patients, of course.

Many of my colleagues ask me often when will this therapy be available for their patients, and many will enthusiastically welcome it as a therapeutic option.

Thank you very much for your attention, and I think I will finish with a few minutes on the clock to spare.

DR. HURST: I would like to thank the sponsor's representatives for their presentation.

Does anyone on the Panel have a brief clarifying question for the sponsor? Please remember that the Panel may also ask the sponsor questions during the Panel deliberations this afternoon.

Dr. Engel.

DR. ENGEL: I'd like to ask Bob Fisher, you mentioned there were six patients, six subjects, excuse me, who were seizure free. If you use the surgical definition of free of disabling seizures, so you don't count non-disabling auras, does that number increase?

DR. FISHER: Yes. We prefer to use the angle classification, if it's all right with you, of surgical results. We didn't, in the double blind study, track the category of disabling versus non-disabling seizures. You may recall that in some of the pilot studies, we commented that stimulation had reduced seizures capable of falls, but it was just too hard to track in a multicenter trial. So I can't tell you specifically about disabling seizures.

DR. HURST: Yes, Dr. Privitera.

DR. PRIVITERA: For a clarification question on the presentation by the statistician, there was a slide that showed the outlier, and on the Y axis, you said these were categories, and I was trying to look at the slide and understand those. Could you clarify what was on the Y axis on those two graphs?

DR. ROCHON: There are a number of plots come out of the PROC GENMOD, slide up please, for looking for outliers in the analysis. One of these, and I'm having trouble reading it, too, is I think Cook's D, distance is one of the criteria, and the other one is the change in the beta parameter for the treatment effect that comes out of either, from the analysis with that individual in or that individual out of the analysis.

So what one would expect is that if the individual is not an outlier, removing that individual from the analysis shouldn't have very much of an effect relative to the other patients in the analysis. If you see a large effect, as you see up here, then it means that that individual's data are very unusual compared to the other individuals. Does that answer your question?

DR. PRIVITERA: Yes. Thank you.

DR. HURST: Yes, Dr. Ravina.

DR. RAVINA: I just want a clarification on the rationale for the duration of the blinded period. I think it was mentioned that part of the concern was how long medications could be kept constant, but is it correct, you said, that medications were held constant during the unblinded period as well? Could you discuss that?

DR. FISHER: Very observant of you to notice that. The difference is, the reason I speculate that we were able to keep medications constant, which is to say only two had new medications added, although some others had medication dose adjustments during that time, during the nine-month unblinded, is because we were doing something for the patients. We had added stimulation, and they knew we were doing something. If they had been asked for an additional three months, making a total of 10 months, where they knew we were doing nothing for their seizures, it would have been a managerially, clinically, and ethically impossible circumstance. Does that answer the question?

DR. RAVINA: Yes.

DR. HURST: Dr. Barker.

DR. BARKER: The sponsor showed information showing that the number of patients with a 50 percent reduction in seizures during the blinded phase was no difference between active and control. Do you have additional information about the number who had a 25 percent reduction in seizures or a 75 percent reduction in seizures?

DR. GRAVES: Yes, we do. Specifically and especially over the unblinded phase. I'm going to ask Dr. Fisher to come back up and describe that.

DR. BARKER: My question was specifically about the blinded phase.

DR. FISHER: Yes. Responder rate is not a very sensitive measure, and we didn't show a very good responder rate differential between the two groups on the high end because the seizure improvement was often less than 50 percent, and then when you get to the lower fractions of improvement, as you're asking about, there often was a significant number of people in the control group who also showed that degree of improvement. We do have a statistically significant difference in month 3 for 30 percent responder rate and for 20 percent responder rate, and we do have good outcome in the long term for responder rate.

DR. HURST: Yes, Dr. Ravina.

DR. RAVINA: A statistical question. One of the most significant predictors in the model that you showed was baseline seizure frequency. My question is should that be interpreted as regression to the mean, or is there another way to interpret that? And is there an interaction between treatment and baseline severity?

DR. ROCHON: I think the answer to your first question is no, I don't believe it's regression to the mean. What we are doing is adjusting for the variable number of seizures across the different subjects that occurred during the baseline phase of the study and standardizing it to the average among those individuals during the baseline phase of this study.

I'm not aware of an analysis that looked at treatment by baseline interaction, but if you will allow me a second, I can just confirm with the company statistician, if you, please.

So that's correct. That analysis was not performed.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: This was a young population. How long does the battery last, and were there any problems with the leads fracturing or requiring repair after implant?

DR. GRAVES: The longevity of the battery is very dependent upon the stimulation parameters that are set by the patient. In general, the battery at the stimulation settings that were used in the blinded phase, the 5 volts, 1 minute on, 1 minute off, was about three, four years on most patients, and some patients as they started to change the cycling settings in the longer term follow-up phases of the trial, that battery longevity went down in some cases, and in some patients when they were adjusting stimulation parameters, it actually went up a bit.

In terms of lead fractures, I don't believe we had any lead fractures. We did have some extension fractures, and I believe that data is in there, and I'll get data up in a second to show you.

Slide up, please.

DR. HURST: Dr. Chugani.

DR. GRAVES: Hold on.

DR. HURST: I’m sorry. Go ahead.

DR. GRAVES: Can I just complete?

DR. HURST: Sure.

DR. GRAVES: Yeah. So this is the extension fracture rate. So that's the part that goes down the side of the neck. In SANTE, we had an extension fracture rate of 3.6 percent. In a similar study in Parkinson's disease, that was about 1.9 percent, and in a tremor study where it's only a unilateral implant, it was about 0 percent. So we did have a 3.6 rate of extension fracture in the SANTE study. Slide down, please.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I have a couple of questions about patient selection and the rationale for selecting patients. I heard at least one case of an encephalitis. I assume that was early in infancy or childhood. And when you talk about the circuitry of Papez, the epileptic circuitry, I think it sort of stands to reason that seizures that are established very early in childhood and maybe in the infancy stage are likely to have a very different epileptic network from those who have onset post-puberty. Did you take this into account in patient selection?

DR. FISHER: That's a very good question. We didn't. Might I assume, Dr. Chugani, from what you're saying, that perhaps you consider that patients with encephalitis might be more severe or more difficult to control than others?

DR. CHUGANI: No, I'm going back to the old, you know, cell that fire together, wire together concept, and we know that that's very different very early in childhood, at a time when there are an exuberance of connectivity in the brain. And post-puberty, partial epilepsy, secondary generalization, it's a much easier concept to understand than I think very early onset seizures.

DR. FISHER: Yes.

DR. CHUGANI: And I'm just wondering whether that kind of aberrant circuitry, they're both aberrant, but in different ways, might account for perhaps some unexpected effects.

DR. FISHER: Yes, it could, and we certainly have no subgroup analysis by etiology. We have 10 patients in the trial who did have encephalitis. By coincidence, you will hear from two of them today, and certainly they were able to be responsive to the therapy as were the others.

I think your point is very cogent. We don't have time in the setting to discuss mechanisms of stimulation, but it's certainly not as simple as just inhibiting a circuit or exciting a circuit. It is a network modulation process with disrupting synchrony with disrupting spread, and therefore if you have a modified circuit at the start due to events early in life, then it could have different effectiveness for those subtypes. The observation was though that for the 10 patients who did have encephalitis as an etiology in our study, the treatment worked as with others.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Since there's a big focus on the statistical analysis regarding the data from Patient A, I have a few questions related to Patient A. First of all, had that patient had a VNS previously, and had there been any kind of frequency seizure relationship seen in that patient previously if they had a VNS?

DR. GRAVES: Dr. Sandok can answer that.

DR. SANDOK: No and no.

DR. PAOLICCHI: Okay. The next questions are really to the sponsor, which is had there been any other kind of analysis of this acute symptomatic seizure initiation with the earlier trials, number one, and number two, has this been reported at all in patients with Parkinson's disease who receive the DBS?

DR. GRAVES: In the pilot patient trials, we did not receive any reports. These are physician-sponsored trials, and none of the physicians mentioned that they had seen this sort of event, and I don't believe that we've seen any of those sorts of events in DBS. I'll look to Dr. Ravina to see if he knows of any, but, in fact, I'll have Dr. Kaplitt perhaps because he has some expertise in DBS.

DR. KAPLITT: Hi, I'm Mike Kaplitt. I'm the Director of Functional Neurosurgery and Vice Chair for Research at Cornell Medical College, and I was a SANTE investigator and am a consultant to Medtronic for this filing.

There had been isolated cases of transient seizures that don't appear to be directly related to stimulation. In most cases, remember Parkinson's and tremor patients don't have seizures at baseline. So I've had patients who had perioperative seizures like any surgery but not really related to stimulation.

However, stimulation-related adverse effects similar to what was described earlier are seen commonly in deep brain stimulation. The best examples are paresthesias that you often see with essential tremor because of the location of the sensory area of the thalamus, near the motor territory. So patients will get paresthesia, you then lower the stimulation and the paresthesia gets better but the tremor is worse, but over time, you can then raise the stimulation back up again and they don't get the paresthesia because the brain becomes tolerant and their tremors get better. That is very analogous to what was described with this very patient. So we do see similar things. Does that answer?

DR. PAOLICCHI: Uh-huh. If I could have one more follow-up question as well because I was concerned about the reports of depression and memory impairment in the patients with the implanted DBS for epilepsy. How does that compare with the data for patients who have an implant for Parkinson's disease and, of course, I am aware, of course, of the increased incidence of depression in that disorder as well.

DR. GRAVES: I'm going to have Dr. Alexander Troster come up and speak to that.

DR. TROSTER: Good morning. I'm Alex Troster. I'm a neuropsychologist and Professor of Neurology at the University of North Carolina. I'm a paid consultant for Medtronic, and I've also previously received an educational grant from them. However, I have no financial interest in the company.

The question you posed is a very good one. I'm not sure there's direct comparability between the epilepsy and the Parkinson's disease population in terms of cognitive deficits. Most of the neuropsychological studies show that there's a relatively low incidence. However, if one defines cognitive changes, including verbal fluency in patients, up to about 20 percent of patients with Parkinson's disease can have changes in verbal fluency that seem to persist even up to three to five years after implantation. Does that answer your question?

DR. PAOLICCHI: And what about the depression?

DR. KAPLITT: The depression mechanism really isn't known. The incidence rate is relatively low as far as we know, but the questions have been raised about suicidality. There's been speculation that the depression might be related, at least in animal models, to depletion in serotonin, but we just don't know that for epilepsy at this point.

DR. HURST: Yes, Dr. Good.

DR. GOOD: A couple of your slides suggested that there might be an age effect. Is it worth talking a little bit more about clarifying that?

DR. GRAVES: I'm going to have Dr. Rochon come up and talk about that.

DR. ROCHON: The analysis, we performed an analysis looking for covariates to include in the model. Age is one of the covariates that came out as related to the outcome measure and was therefore included in the model. I'm not really qualified to answer the question of why there might be a relationship with age other than to say it was important to include in the model. Is there another -- does that answer your question, or are you looking for something different?

DR. GOOD: Well, I'm just thinking whether this would affect indications for the procedure if it was a major effect. Is it something that should be taken into consideration? Probably not because it's a fairly young population, but just your comments.

DR. HURST: Dr. New.

DR. NEW: So through the unblinded phase, you had 40 patients or just over 1/3 with serious adverse events. Did you learn anything from the study so that if the device is approved, going forward we can lower that number, the initial stimulation parameters, anything about the way, you know, it was handled?

DR. GRAVES: Good question. I'm going to have Dr. Labar come up and discuss that with you.

DR. LABAR: Hello. I'm Doug Labar from Cornell. I was the investigator for this study, and I'm a consultant for Medtronic.

So the question is, is there something to do about adverse events that we can learn from the events in the unblinded phase?

Clearly, let me take a step back about some of the things we mentioned upon initiation of stimulation, which would be both in the blinded phase and unblinded phase. Potentially adjusting stimulation parameters would be a good approach. Can I have the slide up?

In terms of serious adverse events that occurred, in the operative phase, which is right after you put the stimulator in through the unblinded phase, the ones that we heard most commonly were the lead's not in the target, and as we go along, we'll continue to try to improve methodology for making sure that they get in the target with greater experience for this implantation approach.

A couple of other things that occurred in the unblinded phase and operative phase which were pretty infrequent, kind of unavoidable, post-procedure pain and so forth.

Can I have the next slide? 18.

As you can see, if you look through the operative phase and through the unblinded phase, most of the adverse events which we thought were related, or the investigators thought were related to the device, were those that occurred in the very first month. This graph shows the reported adverse events per month over those time periods, and a really lot of them, that first bar, that blue bar there on the left, are the adverse events that occurred immediately after the operation in the operative phase. Does that answer your question?

DR. HURST: Dr. Paolicchi.

DR. GRAVES: As a follow-up, if you would care, since a lot of those are in the operative phase, I might have Dr. Michael Kaplitt come up and explain a little bit more, too.

DR. KAPLITT: The only thing I would add is that the one thing that's somewhat unusual about this population compared to most of the DBS patients we've operated on over the last 15 years is that a disproportionate number of these patients have had prior surgery, VNS placements, cranial surgery. Most tremor and Parkinson patients, of course, do not, and I do think, I know in my own practice, in the patients we treated and I think across the board, that there was a bit of a learning curve in terms of the asymmetry of the brain; if they've had a large prior resection, you have much greater asymmetry in the target than you do in Parkinson's, and also the events in terms of infections and wound breakdowns, et cetera, often I think were related in part to old wounds that had been sort of complicated on the operative side, and as we thought more about this, I think that the rates did come down. So I do think that that did help us going forward.

DR. NEW: So, Dr. Kaplitt, did you often take out the VNS right at the same time you were putting in this device?

DR. KAPLITT: I personally did, yes, and most investigators did, and I tried in most cases, except one, to put the pulse generator on the side opposite --

DR. NEW: Opposite, okay, that's what I was wondering.

DR. KAPLITT: -- where the VNS was. I had one patient who used shotguns and --

DR. NEW: And didn't want it there.

DR. KAPLITT: -- he braced it on the shoulder where I wanted to put the pulse generator. So we had to put it at his VNS site and, of course, he had an infection, but then he got better and did well.

DR. NEW: Okay. Did you reopen the neck incision on those VNS patients to trim the leads?

DR. KAPLITT: Yeah, we did not. There is a discussion because the VNS manufacturer has specific labeling --

DR. NEW: Right.

DR. KAPLITT: -- now that asks you to do that, and that is part of the labeling that was included here, but we did not as part of this study because it wasn't part of the labeling then.

DR. HURST: Yes. You had a follow-up question?

DR. PETRUCCI: This is in relationship to the adverse events. Of the reimplanted 9 out 110, were these site related, that is high verse low volume?

DR. GRAVES: I'm going to bring Dr. Kaplitt back up to answer that.

DR. KAPLITT: No, this was really a study learning curve, not a site learning curve. There was no correlation between the experience of the sites either in terms of their prior experience with DBS or their volume of DBS cases or the number of cases they did in the SANTE study. The overall rate of misplaced leads was 8 percent, but in the second half of the study, in the 50 patients or 55 in the second half, it was 3 percent, and I know having done the second case in the study that there were some changes that we made in terms of advising centers because of this asymmetry and the nature of the variability among patients in target that improved over time.

And remember, the other thing is that by protocol, we had to replace any lead where there was not a target that was radiographically determined to be exactly in the site by the study radiologist. In practice, in DBS, if your electrode is a millimeter or two off, you often try to make it work before replacing it, and in all likelihood, that 3 percent rate in the back half will be even lower in practice by doing that.

DR. RAVINA: So the eligibility criteria required six or more seizures per month, but the median in both groups was more than three times that, and it looks like many people no longer qualified during the baseline because of inadequate seizure frequency.

So my question is twofold. One is, can you provide some perspective on whether or not you may have artificially selected a group with a high frequency and the natural history would be to decline? So it's really a natural history question based on the selection. And, two, given the difference between the people who are in the study actually and the eligibility, how do you think about that in terms of the clinical use in terms of seizure frequency?

DR. GRAVES: I'm going to have Dr. Fisher come up and talk about those two points.

DR. FISHER: We intentionally selected patients who had a high seizure frequency, but I don't think that that makes a regression to the mean problem any worse than in any other study because the statistics of the GEE model, and also even in the median ratios, look at all of the data or, in the case of the median ratios, look at percentage improvement.

Dr. Jacqueline French has looked at populations of seizure clinics to see what means refractoriness and how many patients are in that group, and I know we have expertise on that in this Panel as well. Most patients who are called refractory, in most referral populations and clinics, don't have six or more seizure per month. They usually have two, three, four seizures per month or even one seizure per month. So once you get above the six per month criteria, you are dealing with a severely affected population.

Now, we did put an upper cap. You couldn't have more than 10 seizures per day because that is so different that we thought that it might not be reflective of the rest of the population.

And that partially, I think, answers your second question as well, which emphasizes the fact that we are suggesting this treatment not for your Aunt Tilly who had seizures last Sunday, but for an unusually severe and refractive epilepsy population.

DR. GRAVES: One more piece of information regarding that. In terms of the patients that were discontinued during the baseline phase for low numbers of seizures or more than 30-day seizure free, that was 7 out of 47 patients.

DR. HURST: Dr. Barker.

DR. BARKER: I have a question for the statistician following up on that. You have patients in this trial who had 6 seizures per month going in, and you had others up to 300 per month going in.

DR. FISHER: 600.

DR. BARKER: 600 per month going in. And you implied that the FDA suggested a reduction in seizure count as the primary endpoint. Obviously if somebody with 6 seizures per month has 5 fewer per month, that's a big difference in their life, but somebody who has 600 a month, who then has 595 a month, that's not very much difference. Do you think that the GEE model even with the log link and the negative binomial distribution and the lack of robustness that we've seen to a single clinical event that lasted two days, do you think that's the best form of analysis for this type of trial going in the future for other sponsors?

DR. ROCHON: Well, the short answer is yes, I think this was the most appropriate model for us to use. It allows us to analyze data using the log link, which reduces the sort of range, the scope, and the number of seizures that occurred during the course of this study, and using the baseline covariates as the baseline number of seizures was also important for us to account for variability across the individuals in this study. So, again, I would think this was the best model that we could use for this analysis.

DR. BARKER: You don't think that something that used percent reduction in seizures as the primary measure of success wouldn't be better?

DR. ROCHON: You know, we presented those data because it's easy to understand percent reduction in seizures. It also normalizes according to the number of seizures experienced by patient at baseline, and we believe that that's important to do. But we also felt that it was more important to use a model that allowed us to bring in covariates and allowed us to reflect the longitudinal nature of the data and to reflect the protocol that aggregated the number of seizures to these monthly visits during the blinded phase of this study. So, again, I think it reflected properly the design of the study.

DR. HURST: Other Panel questions?

Thank you. We'll now take a 10-minute break. Panel members, please remember that there should be no discussion of the PMA during the break amongst yourself or with any member of the audience.

(Off the record.)

(On the record.)

DR. HURST: I would like to call the meeting to order.

The FDA will now give their presentation on this issue. Mr. Marjenin, you have 90 minutes.

MR. MARJENIN: Thank you, Dr. Hurst.

Good morning, distinguished Panel members, members of Medtronic, Incorporated, and audience members. My name is Tim Marjenin. I'm the Team Leader for the DBS for epilepsy PMA.

Medtronic has submitted a premarket approval application supplement to FDA for the Deep Brain Stimulation System for Epilepsy. This marketing application describes the safety and effectiveness of the device system which is designed to reduce seizures in adult patients with epilepsy that is characterized by partial-onset seizures. The applicant conducted a clinical trial, IDE G030065, in order to assess the safety and effectiveness of the device system.

FDA has reviewed the premarket application supplement for the Deep Brain Stimulation System for Epilepsy, and because this is a new indication for deep brain stimulation, we are seeking Panel members' expertise and input at an open public meeting of the Neurological Devices Panel.

The FDA staff members involved in the review of P960009, Supplement 68, are shown here. And just to give you a quick outline of our presentation, following this introduction and a very brief overview of the device system itself, Dr. Costello will present a clinical summary. Next, Mr. Van Orden will outline the statistical analyses, and finally, Dr. Soldani will discuss post-approval plan considerations.

The DBS system includes, as Medtronic has mentioned, both implantable and external components as listed here. And when the study commenced in 2003, the sponsor used the Kinetra DBS System, which has PMA approval for the following two indications: one as an adjunctive therapy in reducing some of the symptoms of advanced Levodopa response of Parkinson's disease that are not adequately controlled with medications; and, two, for the suppression of tremor in the upper extremity in patients who are diagnosed with essential tremor or Parkinsonian tremor that is not adequately controlled by medications.

The sponsor submitted the Activa PC for approval in 2008 for the Parkinson's disease and essential tremor indications, and it was approved for those indications in April of 2009. Although the Activa PC System was not used in this study, the sponsor wishes to use this system for the indications under discussion today.

Compared to the Kinetra System, the Activa System includes a smaller IPG, the ability to stimulate using both constant current and constant voltage, and additional programmability options. The basic functionality and stimulation limitations, however, are the same for both systems.

Based on our review of the two systems, FDA has concluded that the Activa PC would offer stimulation that is comparable to what was provided by the Kinetra during the study.

Dr. Costello will now present FDA's clinical summary.

DR. COSTELLO: Thank you, Mr. Marjenin. Good morning, members of the Panel.

I will be presenting FDA's assessment of the clinical data submitted in the PMA to support the safety and effectiveness of the Medtronic Deep Brain Stimulation System for Epilepsy. This afternoon, you will be asked several questions that will assist FDA in our determination of whether the device is safe and effective for the proposed indication for use. My discussion will focus on key aspects of the data that are pertinent to these questions.

I will provide a brief study overview that highlights key points that will be important in your discussions today. I will then review the safety and effectiveness data. My discussion of the effectiveness data will focus on the blinded phase of the study limited to a discussion of the prespecified primary effectiveness endpoint, the analyses excluding Subjects A and B, the secondary effectiveness endpoints and the additional outcome measures.

Mr. Van Orden, the statistician, will discuss statistical issues with a primary analysis as well as the sensitivity and long-term data analyses.

Study overview. The study was designed as double-blind, randomized, multicenter, prospective trial. 157 subjects were enrolled at 17 U.S. sites. 109 subjects were randomized 1:1 to either the active group, which consisted of 54 subjects, or the control group, which consisted of 55 subjects. The sample size for the trial was based on an expected 25 percent reduction in seizures for the active group versus the control group.

Following a three-month baseline period, subjects were implanted. Following implant, subjects entered the four-week operative phase. Subjects did not receive stimulation during this four-week phase.

At week four, subjects entered the three-month blinded phase of the study. During the blinded phase, stimulation settings were not allowed to be modified, nor could medications be changed unless the subject experienced adverse events.

At month four, the subjects entered the nine-month unblinded phase. During the unblinded phase, all subjects received stimulation at one of three prespecified sets of stimulation parameters, and antiepileptic drugs were held constant.

During the long-term follow-up phase, there were no limits on stimulation or antiepileptic drugs.

This slide summarizes the stimulation parameters that were used during the trial. During the blinded phase, subjects in the active group received stimulation at 5 volts, 90 microseconds, 145 hertz, cycling 1 minute on and 5 minutes off. The amplitude was set to 0 volts for control subjects.

During the unblinded phase, subjects received stimulation at one of three prespecified settings, either the same stimulations as were used during the blinded phase or changed to a rate of 185 hertz or an amplitude of 7.5 volts.

During the long-term follow-up phase, there were no restrictions on stimulation parameters other than the appearance of a warning if the charge density exceeded 30 $\mu C/cm^2$/phase.

Subjects were excluded if they averaged more than 10 complex partial seizures per day, had an episode of convulsive status epilepticus within the 12 months prior to baseline, had a previous diagnosis of psychogenic seizures, or within 5 years prior to baseline had a psychiatric illness hospitalization, suicide attempt, or symptoms of psychosis unrelated to an ictal state, a postictal state, or a medication.

I would like to highlight three demographic issues. For the 110 implanted subjects, the baseline monthly seizure counts ranged from 6 to 604, the mean was 56.1, and the median was 19.5. We would like you consider the wide baseline range of seizure counts when evaluating the clinical significance of the primary effectiveness endpoint. Forty-nine of the implanted subjects had previously been treated with Vagus Nerve Stimulation therapy. Due to the helical design of the Vagus Nerve lead, removal of the lead is difficult to perform without incurring nerve injury. Thus, at least 48 of the subjects had abandoned Vagus Nerve Stimulation leads.

Please take this into consideration in your deliberations of the following question.

The sponsor has provided MRI guidelines, based on bench and phantom testing, that apply to their DBS system. In addition, the sponsor's proposed labeling recommends that a postoperative MRI be performed to confirm proper lead placement. The sponsor has not provided test data on the MRI compatibility of the Deep Brain Stimulation system with abandoned Vagus Nerve Stimulation leads.

Fourteen lead revisions were required in nine subjects because the leads were not within the anterior nucleus of the thalamus. Do you believe that MRI compatibility testing should be conducted prior to approval to allow a postoperative MRI to confirm lead placement and to allow MRI use for future medical needs? Alternatively, do you believe that the accurate placement of the lead and patient safety can be assured without the option of postoperative MRIs?

Subjects had seizure onset in various areas. This slide provides a breakdown of the areas of seizure onset. The areas of seizure onset exceed 110, since subjects could have seizures from more than one onset location. The majority of the subjects had seizure onset in either the temporal or frontal lobes. Please keep this in mind when considering the proposed indication for use.

Bilateral anterior thalamic nucleus stimulation using the Medtronic Deep Brain Stimulation System for Epilepsy is proposed as adjunctive therapy for reducing the frequency of seizures in adults diagnosed with epilepsy characterized by partial-onset seizures, with or without secondary generalization, that are refractory to antiepileptic medications.

Please take the location of seizure onset and proposed indication for use into consideration in your deliberations of the following Panel question.

All subjects received bilateral stimulation to the anterior nucleus of the thalamus. The proposed indication does not restrict the location of the seizure onset. However, the majority of the subjects' seizures originated in the temporal and frontal lobes.

Do you believe that there are sufficient data to support an indication that encompasses partial onset from any location as well as multifocal onset? Alternatively, do you believe that the indication should be restricted based on seizure onset location? If so, please state the seizure onset location to which the indication should be limited.

I will now discuss the sponsor's safety data. 157 subjects were enrolled into the study. 110 subjects entered the operative phase, and 109 subjects entered the blinded phase.

One subject in the operative phase and one subject in the blinded phase developed infections that required device explant. When the devices were replaced, the subjects entered the long-term follow-up phase.

Of the 110 implanted patients, 90 or 81.8 percent remained active in the study. This includes the one recently reported death.

The trial had two safety objectives. One was to collect information on all the adverse events that occurred during the trial, and the other was to characterize the incidents of sudden, unexplained death in epilepsy or SUDEP.

This slide summarizes the incidence of adverse and serious adverse events that occurred from baseline through long-term follow-up. The sponsor has separated adverse events into device related and non-device related events. However, FDA has not made this distinction as the cause of the event is not always clear.

It should be noted that for an event to be considered a serious adverse event, it had to meet certain criteria such as requiring or prolonging hospitalization or being life-threatening or resulting in a significant disability or impairment of body function. Thus, as you will see in subsequent slides, certain adverse events were severe but did not meet the definition for a serious adverse event.

Over the course of this study, 81.5 percent of the patients reported a total of 1,779 adverse events, and 43.9 percent of the patients experienced a total of 109 serious adverse events. I would also like to point out that during the long-term follow-up, there were still significant numbers of adverse events and serious adverse events in this population.

The remainder of my presentation will focus on the 110 implanted subjects. During the operative through unblinded phases, there were a total of 808 adverse events that occurred in 99.1 percent of the patients, and 55 serious adverse events that occurred in 36.4 percent of the patients. 172 of these adverse events occurred in the operative phase, and 29 of the serious adverse events occurred in the operative phase.

There were six deaths in the study, four of which were determined by the Data Safety Monitoring Board to meet the criteria for SUDEP. One of the deaths occurred during the baseline phase and is not included in the calculation of the study SUDEP rate. Two of the deaths in the implanted subjects met the criteria for definite SUDEP, and the subject who drowned is considered a possible SUDEP. In addition, one subject committed suicide. There has also been a recent additional death, the cause of which is currently unknown.

This table represents the SUDEP rate. The sponsor has calculated the SUDEP rate based on 397 years of stimulation, which includes 72 stimulation years of pilot study experience. FDA has calculated the SUDEP rate based on the SANTE PMA cohort only, and therefore the total number of years of stimulation was 325.

Using data from the SANTE PMA cohort only, the definite probable SUDEP rate was 6.2 per 1,000 person years, and the definite/probable/possible SUDEP rate was 9.2 per 1,000 person years with a 95 percent Poisson confidence interval of 1.9 to 26.98.

Please be aware that if the additional death is determined to be a SUDEP, the rate would be recalculated, taking into account the additional years of stimulation.

Please take the SUDEP rate into consideration in your deliberations of the following question.

The definite/probable/possible SUDEP rate for the PMA study cohort was calculated to be 9.2 deaths per 1,000 person years based on the three deaths that occurred after the completion of the baseline phase. Is this SUDEP rate acceptable for the proposed population?

A total of 20 of the implanted subjects, or 18.2 percent, discontinued the study. This includes the five deaths that occurred in the implanted subjects. No subjects discontinued during the blinded phase. Five subjects discontinued during the unblinded phase, and a total of 15 subjects discontinued during the long-term follow-up phase. Nine subjects discontinued after having received three years of stimulation. A total of five subjects discontinued due to lack of efficacy, one between years one and two and four after three years of stimulation.

Prior to discussing adverse events related to depression, memory impairment, and anxiety, I would like to point out that there were significant numbers of subjects in the active and control groups who had a medical history of these conditions. However, the number of subjects in the active and the control group with a history of these conditions was similar.

There were a total of eight serious adverse events that occurred in the blinded phase. Two subjects in the active group had serious adverse events related to depression and status epilepticus. There were six serious adverse events in the control group. Two were implant site infections. Two were seizure related. There was one subject with an anxiety event and one subject with involuntary muscle contractions.

This table provides a comparison of key adverse events that occurred in the active and control groups. More subjects in the active group than in the control group reported depression, memory impairment, and anxiety. Five subjects in the active group compared to two subjects in the control group reported paresthesia events, implying that subjects were not unblinded due to paresthesia events.

Finally, there were more injury events in the control group. However, Mr. Van Orden will discuss this finding in more detail.

Eight subjects reported adverse events related to suicidality. Six of the subjects had a history of depression or suicide. One subject committed suicide. This subject was not receiving stimulation at the time of the event. For the subjects with the other events, stimulation was on at the time of the event. Two subjects made suicide attempts. Both of these are considered resolved, and one met the criteria for a serious adverse event. Five subjects were reported to have suicidal ideation. Three of the events have resolved, and three met the criteria for a serious adverse event.

Please take the depression and suicidality events into your consideration of the following question.

One suicide occurred during the study. There were seven additional subjects with events related to suicidality, including two subjects who made suicide attempts and five subjects with suicidal ideation. More subjects in the active as compared to the control group reported depression and anxiety. Do you believe that these events raise concerns regarding a reasonable assurance of device safety for the proposed indication?

Five subjects were reported to have asymptomatic intracranial hemorrhage. Five subjects also were reported to have status epilepticus events, two of which occurred during the operative phase, and one event occurred during the blinded, unblinded, and long-term follow-up phases. Four events were considered serious. The other events occurred on the day of the initial implant and thus did not meet the criteria for a serious adverse event. Four of the events were non-convulsive.

Five subjects had seizure-related events that occurred during the first week of stimulation. The first week of stimulation for subjects in the active group would be the first week of the blinded phase. For subjects randomized to the control group, the first week of stimulation would be the first week of unblinded phase.

Three of the subjects had adverse events related to simple partial seizures. One subject experienced confusion and status epilepticus. An additional subject, Subject A, had increased complex partial seizures. This subject will be discussed in more detail in the effectiveness presentation. Please take the status epilepticus and seizure-related adverse events into consideration in your deliberations of the following panel question.

Five subjects experienced status epilepticus and five subject had seizure-related adverse events that occurred upon initiation of stimulation, including Subject A. Do you believe that these seizure-related events raise concerns regarding a reasonable assurance of device safety for the proposed indication?

Twelve subjects had the complete Deep Brain Stimulation system explanted. The most common cause for explant was infection. Fourteen leads in nine subjects were replaced due to not being within the boundary of the anterior nucleus of the thalamus. Forty-three subjects had a total of 65 IPG replacements due to normal battery depletion. A Kaplan-Meier survival analysis found that 50 percent of subjects would need IPG replacement after 36.8 months of stimulation.

I will now discuss effectiveness. The primary endpoint was to demonstrate that the reduction in seizures in the active group is greater than in the control group, using a generalized estimating equation model. The GEE model accounts for between and within subject variation in seizure counts. The baseline and blinded phases consisted of three 28-day intervals. The number of seizures were recorded for each 28-day interval and was used as a count data for the model. The primary analysis included subjects with at least

70 days of seizure frequency data in both the baseline and blinded phases.

The study failed to meet the prespecified primary endpoint. The p-value was 0.483. This analysis was based on 108 subjects who had 70 days of seizure counts. One subject was excluded since the subject had only recorded 66 days of seizure counts.

This table represents the median seizure reduction. Data on the prespecified GEE adjusted means will be presented in a subsequent slide. At baseline, subjects in the active group had a median seizure count of 18.4 seizures per month while subjects in the control group had a median seizure count of 20.2. At the end of the operative phase, both groups had a seizure reduction of 3.3 seizures. Please note that stimulation was not turned on during the operative phase.

Over the entire blinded phase, the active group had a median seizure reduction of 5.2 seizures while the control group had a median seizure reduction of minus 2.9. Therefore, the overall difference in median seizure reductions was minus 2.3 seizures per month.

The sponsor also prespecified an analysis to determine whether there was a visit by treatment interaction. The monthly median seizure rate decreased over the three months for the subjects in the active group. In contrast, for subjects in the control group, the median seizure rate was stable at minus 4.2 over months 1 and 2, but then increased to only minus 2 seizure reductions from baseline. Therefore, the month 3-4 difference in median seizure reduction was minus 6.5 seizures.

However, as previously stated, the GEE analysis was prespecified as the primary analysis due to monthly variations in seizure counts.

The sponsor has performed two additional analyses. One is the alternative analysis which excludes Subject A who is an outlier. Subject A was randomized to the active group. When stimulation was turned on to the prespecified stimulation settings, Subject A experienced 210 new type complex partial seizures over the first three days of stimulation which equated to 1,347 percent increase. When the stimulation was reprogrammed, from the prespecified amplitude of 5 volts to 4 volts, the new type complex partial seizures stopped and did not recur throughout the remainder of the study. There was no prespecified definition of an outlier, and thus this analysis was not predefined.

The other is a sensitivity analysis which excludes Subject B. The site investigator felt that Subject B's diary data may be unreliable because the subject was diagnosed with psychogenic seizure. The sponsor added the analysis prior to breaking the blind. After the blind was broken, it was determined that the subject had been randomized to the control group.

This table provides a summary of the primary and additional analyses proposed by the sponsor. The p-value, median seizure reduction, and GEE adjusted means difference is provided for each analysis. As you will see, these analyses give slightly different results.

As previously stated, the p-value for the primary analysis was 0.483, and the median seizure reduction difference between the active and the control groups was minus 2.3. The GEE adjusted means difference between the active and the control groups was minus 2 seizures.

If Subject A is excluded, the p-value achieves statistical significance. If Subjects A and B are excluded, the p-value is not statistically significant and is 0.063.

However, it is important to note that the exclusion of Subjects A and B, although they do affect the p-value, have a minimum effect on the median seizure reduction. The median seizure reduction changes from 2.3 to 2.5 and the GEE adjustment mean changes from minus 2 to minus 4 seizures per month.

This figure represents the percent reduction in seizure frequency at the end of the blinded phase for each subject. The green lines represent subjects randomized to the active group, and the red lines represent subjects randomized to the control group.

It is important to note the 10 subjects in the active group had increased seizures, including Subject A, and 16 subjects in the control group had increased seizures. Only one subject became seizure free, and this subject was in the control group.

The study had three secondary endpoints, one of which was to compare the number of responders defined as subjects who had at least a 50 percent reduction in seizures from baseline. Sixteen subjects in the active group and fourteen in the control group met the criteria for a response.

Please take the seizure reduction in the operative phase, the primary effectiveness analyses, and the individual patient data into consideration in your deliberations of the following question.

The sponsor failed to meet the prespecified efficacy endpoint. The sponsor proposed two additional analyses. At the end of the 4 week operative phase, both groups had a median reduction of 3.3 seizures per month. While statistical significance is reached depending on the analysis, the difference in the median seizure reduction between the two groups is less than three seizures per month. Do the data represent a clinically significant difference in seizure reduction between the two groups?

The study had three prespecified secondary endpoints. The secondary endpoints which compared subjects in the active and the control groups at the end of the blinded phase were chosen to further characterize the change in seizure rates. The secondary endpoints included the responder analysis, the number of seizure-free days and the maximum length of seizure-free intervals, and the number of treatment failures. Treatment failures were defined based on the use of rescue medications or episodes of convulsive status epilepticus. Please note that seizures and epilepsy-related injuries were not prespecified secondary endpoints.

P-values for each of the secondary endpoints were greater than 0.05.

Please take the secondary endpoint analyses into consideration in your deliberations of the following Panel question.

The secondary endpoints (responder analysis, seizure-free days, length of seizure-free intervals, and treatment failures) were chosen to support the primary endpoint. All of the secondary endpoints had p-values greater than 0.05. Do the data represent a clinically significant difference in seizure reduction between the two groups?

The sponsor also prespecified a number of additional study measures. These exploratory measures were designed to assess differences between the active and control groups at the end of the blinded phase in the following areas: seizure type and severity using the Liverpool Seizure Severity Scale, number of therapy access controller activations, healthcare resource utilization, and the number of times rescue medications were used. In addition, the sponsor included three patient-reported assessments. These were the Quality of Life in Epilepsy, or QOLIE-31, an assessment which is validated for this population, as well as subject satisfaction and outcome which are not validated for this population. P-values were greater than 0.05 for each of these measures.

As previously stated, subject satisfaction and outcome results were assessed as additional outcome measures at the end of the blinded phase, and the p-values were greater than 0.05. However, it should be noted that more subjects in the control group were either very or somewhat satisfied with the therapy, would go through the treatment again for the same result, and would recommend the therapy to a friend.

The sponsor has presented open label data to support the safety and effectiveness of the device. FDA has focused the efficacy discussion on the prespecified GEE analysis of the blinded phase data. During the unblinded and long-term follow-up phases of the study, subjects knew they were receiving stimulation. Subjects who know they're receiving stimulation may overestimate the benefit, making analysis of open label data difficult to interpret. In addition, subjects were allowed to make changes to the antiepileptic drugs beginning one year after implant, and subjects could drop out if they were not receiving effective therapy.

To summarize effectiveness, the study failed its primary effectiveness endpoint. The monthly median seizure reduction difference was minus 2.3, and the monthly GEE adjusted means difference was minus 2. If Subjects A and B are excluded, the monthly median seizure reduction difference changes to only minus 2.5, and the monthly median adjusted means difference changes to minus 4. At month 3-4, the median seizure reduction difference is minus 6.5, and the monthly GEE adjusted mean difference is minus 6. All of the secondary and additional outcome measures have p-values greater than 0.05, and the unblinded and long-term follow-up phases were open label.

To summarize safety, during the operative through unblinded phase, 99.1 percent of the subjects experienced a total of 808 adverse events, and 36.4 percent of the subjects experienced a serious adverse event.

There were a total of five deaths in the implanted cohort. Three of the deaths were determined to be SUDEP, one was a suicide and the cause of the additional death is currently unknown.

There were seven suicidality events in addition to the suicide. In addition, more subjects in the active than the control group reported depression, anxiety, and memory impairment.

Five subjects had intracranial hemorrhage, five subjects had status epilepticus, and five subjects had events upon the initiation of stimulation.

A total of 15 subjects, excluding the 5 deaths, discontinued, 5 for lack of efficacy.

There were 12 explants, and 9 subjects required a total of 14 leads to be replaced due to not being within the anterior nucleus of the thalamus.

Please take the safety and effectiveness data into consideration in your deliberations of the following Panel questions.

Do you believe that the clinical data in the PMA provide a reasonable assurance that the proposed device is safe and effective for the specified population, and that the benefits of the device outweigh the risks?

The proposed labeling includes a warning that highlights the need for depression monitoring and a precaution to highlight awareness of the potential for increased seizures upon stimulation initiation. Do you believe that these proposed labeling statements adequately address the potential for depression and seizure-related adverse events? If not, what modifications would you recommend?

You will also be asked if you have any other labeling recommendations.

Mr. Van Orden will now do the FDA presentation of the statistical plan.

MR. VAN ORDEN: Thank you, Dr. Costello.

My name is Alvin Van Orden, and I will be presenting the statistical review.

In this plot, the green and red boxes, representing the active and control groups, show the 25th and 75th percentile for epilepsy counts for the active and control groups in different phases of the study. In other words, about 75 percent of subjects had average monthly seizure counts of about 50 or less. The top of the graph, showing the maximum was cut off to allow us to see the majority of the patients more clearly. The minimum is represented by the line below the colored boxes. The dots represent the median seizure counts, and the triangles represent the means. As you can see, the mean is pulled up towards the maximum, and when the mean is unadjusted, it is not very representative of the overall population.

This plot is the same as the one in the previous slide, but it is zoomed out to allow us to see the maximum. Some subjects had as many as 500 seizures per month even after three months of active treatment.

As you see the summary of the results of this study, keep in mind that this is a very diverse patient population.

Here we have the prespecified GEE model or generalized estimating equation. This model tries to predict the log of seizure counts and using the log as a scientifically valid method of dealing with some of these extreme cases. The model adjusts for the treatment group visit and treatment by visit interaction, meaning that the effective active treatment could be different at various time points. The model also accounts for baseline seizure counts and baseline covariates.

The primary hypothesis was that the active treatment would show improvement over the entire three months when adjusted for the three months of baseline seizures. The model was built to allow for interaction, meaning that one of the three might show different results from the other two, but the primary hypothesis was to show an overall difference.

The model is predicting the log of seizure counts adjusting for baseline seizure counts, and in building the model, we only want to keep the covariates that are most important. It was prespecified that covariates would be included in the model using the p-value cutoff of 0.1. However, it was also prespecified that statistical significance would be determined based on a comparison to the 0.05 level.

Here are the results of the primary analysis. The terms on the left are parts of the model we want to focus on. If the interaction were significant, then one would look at each month individually and focus on the significant effect at month 3-4. However, the treatment by visit interaction is less than .1 but is not less than .05. Thus, it may be included in the model but the interaction is not statistically significant. The important term is the overall treatment effect, which has a p-value of 0.483.

Down at the bottom, we have included the estimates if the interaction term is not included. As you can see, the model estimate has a two seizure difference overall.

As I just mentioned, the prespecified model does not show statistical significance, though the interaction is close to the cutoff for statistical significance. The log of baseline seizure counts was highly significant, meaning baseline seizure counts are highly predictive of counts during the blinded phase.

The sponsor also included the log of age in their final model. However, upon further examination and consultation with the sponsor, we don't believe that age has a clinically relevant impact on the effectiveness of the investigational device.

Subject A has been discussed previously by both the sponsor and Dr. Costello. The FDA agrees that Subject A is an outlier, not because of the number of seizures but because of the extreme percent increase in seizures in a short window of time.

However, we urge some caution in simply removing Subject A from any analysis. As has been discussed previously, other subjects had changes in seizure types and/or frequency upon initiation of the treatment even if they did not experience such an extreme change. There's no assurance that future patients will not experience similar results. Subject A's experience may be unusual, but it may be representative of a small part of the population's reaction to the initiation of stimulation.

Here we see the adjusted means and confidence intervals for the three months of the blinded phase. Please note that since these means are adjusted, using the GEE model, that they are appropriate to use and are close to the medians.

Please note how large the confidence is when Subject A is included in the study. By contrast, when we remove Subject A, the confidence interval shrinks dramatically and we see a modest decrease in seizure counts across all three months. The consistency from month to month in this graph, as compared to the previous graph, is what leads to a dramatic change in p-value. When we look at the GEE model without Subject A, we find that the main effect for the active treatment is statistically significant at 0.043.

We do not consider Subject B to be an outlier, but when we also remove Subject B, whose data was considered unreliable by a blinded investigator, then we see that the model is not statistically significant, though it is close. It is inappropriate to get hung up on small changes in the p-value as the difference in the level of evidence between the p-value of 0.43 and 0.63 is very small. However, given that the data from Subject B was considered to be unreliable by a blinded investigator, it is the opinion of the FDA that if you're going to remove subjects from the primary analysis, it is more appropriate to remove A and B than just A. Again, one should use caution in throwing out data.

When you look at the GEE mean seizure counts and the median seizure reduction, we urge you to look at these differences in the context of the baseline means and medians, not in comparison to the range of baseline seizure counts. While there is a large difference in overall p-values between the primary and alternative analyses, the difference in medians and adjusted means is not that large. The increased seizures in Subject A is important, but we warn against making a decision based on either the inclusion or the exclusion of a single subject.

In addition to the primary analysis, the sponsor provided the following prespecified sensitivity analyses, as the subjects who turned off the device for periods of time, some subjects in the active group did not receive treatment 100 percent of the time as scheduled. However, removing these subjects did not change the results. None of the analyses listed here showed a statistically significant treatment effect.

The first of the secondary endpoints had two parts, seizure-free intervals, or the longest amount of time between seizures and seizure-free days. There was a small improvement in the number of seizure-free days, but the difference between active and control was not statistically significant.

There were no failures in any of the subjects in the blinded phase, and the results were not significantly different.

A responder was defined as improving by 50 percent or more from baseline. The proportion of responders was not significantly different between the active and control groups.

And this graph, showed previously by Dr. Costello, we see the percent increase or decrease or the percent change in both the active and control groups. This line represents the 50 percent difference, which was prespecified as the cutoff between responders and non-responders. Changing the definition of responder does not change the outcome. At any definition of responder, there is no significant difference in responder rates between the active and control groups.

This plot shows the median seizure counts for every month from baseline to the end of the unblinded phase. Note how there are large changes in the median seizure counts even within the baseline and operative phases. Also note that the control group shows an immediate decrease in the median seizure count, but from month 4-5 to the end of the unblinded phase, the median seizure counts for both treatment groups remains fairly stable.

Month 3-4 is important as it is the last month of the blinded phase. Regardless of whether Subjects A or B are included or not, there was a reduction in seizures in the treatment group. It is unclear how we should interpret this difference.

Recall that the study was designed to collect three months of baseline seizure data because it was known that seizure rates are highly variable. Also, the study was designed to exclude all patients that didn't record at least 70 patient days during the blinded phase, believing that less than 70 days was not sufficient information.

We saw on the graph on the previous slide that there was a lot of variability from month to month. This variability helps explain why the treatment effect and treatment by visit interaction were not statistically significant despite the difference observed in month 3-4.

Finally, when the control group began receiving stimulation at the beginning of the unblinded phase, the control group patients did not follow the same pattern of improvement as the active group patients.

The Panel will be asked the following question.

The primary analysis compared the data averaged over a three-month baseline period to the data averaged over a three-month blinded phase. This approach is preferred because it's less susceptible to monthly variations in seizure counts. The sponsor has provided an analysis that compares the active and control groups in the last month of the blinded phase to the average three-month baseline period.

Given the month-to-month variability, does the comparison of data from the last month of the blinded phase to the three-month baseline data provide adequate assurance of safety and effectiveness for an epilepsy indication?

If not, how long should the blinded phase be in order to provide a reasonable assurance of the effectiveness for a deep brain stimulation device?

This table shows a breakdown by seizure type. Not all subjects in the study experienced all types of seizures. So the sample sizes for the simple, complex, and generalized seizures are smaller than the overall sample sizes. Since the category of most severe seizures is specific to each patient, then each patient must experience his or her own most severe seizure.

The sponsor eliminated subjects that did not have a most severe seizure at baseline. However, some subjects did not have a most severe seizure at baseline but did have one during the blinded phase. In these cases, subjects were reported as having a 100 percent increase in seizures. Including all of the available information leads to the results shown in this table. Thus, while there was a trend toward a reduction in complex and severe seizures, a statistically significant difference was not found.

This graph is the graph of the complex partial seizures during the unblinded phase, and you will see that the active group in green continued to have a larger reduction in complex seizures even after the stimulation was turned on. This suggests that the difference in complex seizure rates between the active and control groups may not be due to stimulation but to some other unknown cause.

To summarize this point, the reduction in complex and severe seizures is close to the typical cutoff for statistical significance. However, since this analysis was not designated as a primary or secondary endpoint, the Type I error rate is not controlled, and 0.05 may not be the appropriate cutoff.

Also, the active group continues to have lower rates of complex partial seizures suggesting a difference between the two groups may be due to something besides the act of stimulation.

This graph shows the overall quality of life from the QOLIE-31 questionnaire. This was an additional endpoint. This graph shows the mean quality of life for the control group in red and the active group in green and the combined 95 percent confidence interval in blue. Higher scores are better, and scores can range between 0 and 100.

You'll note that the control group had a higher quality of life score throughout the study, and the control group had a higher change from baseline than the active group at month 4, which is the end of the blinded phase.

You will also note that there was a larger change in the quality of life between the baseline and the end of the operative phase than there was between the operative phase and the end of the unblinded phase.

Thus, while the change from baseline to the end of the unblinded phase was statistically significant, there was a larger improvement in the quality of life by implanting the device than by turning the device on.

Subjects may enroll in a study when seizures are at their worse. Recall that subjects that did not have enough seizures at baseline to meet inclusion criteria were discontinued from the study. Under such conditions, some improvement may be attributed to regression to the mean. Also these subjects knew that they were being studied, and after four months, they knew they were receiving treatment. All of this knowledge positively impacts the results, and the long-term follow-up data is harder to interpret because some patients begin to withdraw from the study and changes in medication are allowed.

The Panel will be asked the following question.

The PMA contains data on all available subjects for two years or more post-implant. The sponsor believes that effectiveness is supported by the open label phases. FDA believes that the open label data are difficult to interpret.

Given that the unblinded and long-term phases were open label, subjects could change their antiepileptic medication, subject could change their stimulation settings, and there were missing data. Please provide your interpretation of the open label data.

This slide summarizes the adverse events for which there was the largest difference between the active and control groups during the blinded phase. The active group had higher rates of depression, memory impairment, and anxiety. The control group saw higher rates of injury.

In the most recent PMA supplement, the sponsor had combined injury, contusion, and excoriation, combined these adverse events and found that there was a significant difference between the active and control groups. The sponsor has continued to update their definition of seizure-caused injuries, which explains a small difference between the results in their presentation and the ones shown here.

This table shows that there was a decrease in injury in the active group from two per month at baseline to one per month in the blinded phase. The main reason why there was a significant difference in injury events between the active and control groups is because the control groups had a sudden increase from 2.7 in the baseline to 5.3 in the blinded phase, and comparing the baseline injury events to the unblinded phase, the difference between the active group's baseline and unblinded phase is only .1 event per month in the active group.

The Panel will be asked the following question.

Do you believe that the clinical data in the PMA provide a reasonable assurance that the proposed device is safe and effective for the proposed indication, and that the benefits of the device outweigh the risks?

I will now turn over time to Dr. Soldani who will discuss the proposed postmarket study.

DR. SOLDANI: Good morning, distinguished members of the Panels and members of the audience.

My name is Federico Soldani, and I'm one of the epidemiologists in the Division of Epidemiology in the Office of Surveillance and Biometrics at the Center for Devices and Radiological Health at FDA and epidemiologist on the premarket application review team.

I will now present the post-approval study considerations for the DBS System for Epilepsy.

Before we talk about post-approval studies, we need to clarify a few things. The discussion of a post-approval study prior to formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel should find the device approvable. The plan to conduct a post-approval study does not decrease the threshold of evidence required to find the device approvable. The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating the reasonable assurance of safety and effectiveness in order for the device to be found approvable.

There are two general principles for post-approval studies. The main objective of conducting post-approval studies is to evaluate device performance and potential device-related problems in a broader population and over an extended period of time after premarket establishment of reasonable assurance of device safety and effectiveness. Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

The reasons for conducting post-approval studies are to gather postmarket information, including long-term performance of the device, including the effects of retreatments and device changes; data on how the device performs in the real world in a broader patient population that is treated by community-based physicians and specialists as opposed to highly selected patients treated by investigators in the clinical trials; evaluation of the effectiveness of training programs for use of devices; and evaluation of device performance in subgroups of patients since clinical trials tend to have limited numbers of patients or not patients at all in certain vulnerable subgroups of the general patient population. In addition, post-approval studies are needed to monitor adverse events and outcomes of concern, including effectiveness, especially rare adverse events that were not observed in the clinical trials.

Finally, post-approval studies should account for panel recommendations.

Postmarket considerations important for DBS System for Epilepsy are: What is the long-term effectiveness of this device on seizure reduction? What are the safety issues related to device implant and stimulation once it is used in a larger patient population and used by a diverse group of physicians?

This table presents an overview of the applicant's proposed post-approval studies. The study's objectives will be to evaluate device long-term safety and sustained treatment effectiveness. The applicant proposes to continue follow-up of the premarket cohort.

The study will be (1) an extended follow-up of the premarket SANTE cohort and (2) a multicenter, single arm, open label study of new subjects. There is no specific study hypothesis formulated in the protocol.

About the study population and sample size, the goal is to have 100 implanted subjects at the end of the five-year follow-up. The samples for the two proposed studies would consist of all 90 subjects in the SANTE cohort and a minimum of 120 new subjects, respectively.

Follow-up of 200 plus subjects to be followed for 5 years post-treatment, expecting that at least 100 of these will complete follow-up.

The primary effectiveness endpoint will be reduction in seizure frequency compared to baseline, at yearly intervals as measured in the three-month period prior to the conclusion of each year.

And the safety endpoints would include all adverse events evaluated at six-month intervals, including device implant procedure and calculated adverse events. All serious adverse events, regardless of cause and deaths, including SUDEP, sudden unexplained death in epilepsy, would be evaluated.

The applicant described the post-approval study plans earlier. We would like to bring to your attention a few issues regarding the proposed post-approval studies.

First, the post-approval study's questions and hypotheses are not specified explicitly. Second, the sample size proposed is not hypothesis driven. Third, no detailed statistical analysis plans were provided in the post-approval studies protocols presented. Fourth, no comparison group to allow valid assessment of safety or sustained effectiveness was proposed. Finally, no inclusion of specified subgroups was proposed.

In the event the DBS System for Epilepsy is approved, FDA will continue to develop the post-approval studies protocols interactively with the applicant.

Based on the applicant's proposed post-approval studies and our initial assessment, we will be asking the Panel members during your afternoon deliberations to discuss whether the proposed post-approval studies plans are appropriate to evaluate sustained treatment effectiveness and long-term device performance in the -- population and to make recommendations accordingly.

In particular, we will be asking the Panel to address the following issues.

The sponsor has not proposed a comparison group (for instance, best medical therapy), and instead intends to use a subject's baseline seizure rate as a measure of sustained effectiveness. Please discuss if there is a need for an active comparison group, and if so, please make a recommendation on the most appropriate comparator.

Among the adverse events in the premarket study and postmarket experience for currently approved indications, there were a number related to depression, suicidality, memory impairment, and seizure activity. Please discuss if such endpoints should be included in the evaluation of the postmarket device performance.

The SUDEP rate was 9.2 deaths per 1,000 patient-years in the premarket study with a confidence interval going from 1.90 to 26.98. Please discuss what would be an acceptable threshold for the rate of SUDEP in the post-approval study.

The current proposal does not include any subgroup analysis. Please discuss whether the study should include subgroups such as those who have, for instance, various sites of seizure onset, failed VNS therapy, prior ablation/resection procedures, subjects between ages 18 to 21, or other subgroups.

This concludes my presentation as well as FDA's presentation this morning, and we would welcome any questions that you may have.

DR. HURST: Questions from the Panel? Dr. Engel.

DR. ENGEL: This went by very fast, but I noticed that there were discrepancies at times between the numbers that Dr. Costello said and the numbers on the slides, and sometimes the numbers on the slides didn't add up. Are the slides correct or what you told us correct?

DR. COSTELLO: Could we go to the slide that you're talking about?

DR. ENGEL: There were a lot of slides.

DR. COSTELLO: Okay. Well, I can tell you that there's been a recent death. So when I talked about the number of patients who were still enrolled in the trial, I tried to say that we included the recent death, although that was not included in the sponsor's last PMA supplement. So there were a total of 90 patients that are continuing in the trial.

DR. HURST: Excuse me. Dr. Eydelman.

DR. EYDELMAN: I'm sorry. Yes, hi, this is Dr. Eydelman. I think I can address this. The information on the slides is correct. I think you misspoke a couple of times, Ann, and I think that's what you were referring to. The information on the slides that you have in your handout is the correct numbers.

DR. HURST: Thank you. Dr. Ravina.

DR. RAVINA: It was noted that there was no significance to the responder analysis despite the cutoffs that were used per responders. Can you just say what the different rates were that you looked at to define responders?

MR. VAN ORDEN: I just looked at major, rounded numbers of 50, 40, 30, et cetera.

DR. HURST: Yeah.

DR. NEW: You know, the controversy in this data that we've gone through now in a lot of detail looks at the overall response between this active group and the control group in the blinded phase, and we're looking at it -- I think it's being looked at, I should say, as if it's a drug trial and the control patients received a placebo or sugar pill, but that's actually not what this is.

This is a device implant trial, and there's some positive effect of the implant. That's not a bad thing. We know how these devices work. They work through inhibiting the nucleus where they're implanted and there's some lesion effect. Dr. Fisher referred to it or alluded to it in his discussion, but I don't think there's been much discussion overall of the fact that the control patients had a positive effect. The active patients had a slightly more positive effect, and we can, you know, argue all day about the statistical significance, clinical difference, or whatever, but as a Panel trying to review this device, are we supposed to -- essentially what you had was a control group receiving part of the therapy and an active group receiving the full therapy, and they both benefited. Are we supposed to ignore the implant effect, the positive implant effect that the device had?

DR. EYDELMAN: If I can just add to that. We're here seeking your input on the safety and effectiveness of the device, not the procedure that is used to generate a particular lesion, i.e., if you could do a surgical procedure and just generate the lesion without implantation of a device --

DR. NEW: I agree. That wasn't being studied. It was not a lesion study. But the fact is that implanting the device has two modes or what I would argue is that there's two modes of positive effect with this therapy, which by necessity does involve implanting the device. There's some small positive effect from implanting the device, and there's an additional slight, whether it's significant or not, positive effect of turning the device on, and so, you know, I think that the therapy, if approved, would obviously include both of those, and I think it's a benefit of looking at the unblinded portion of the trial, the overall positive effect of the therapy on the whole population. You know, I'm just looking for input on what your opinion is on looking at it that way.

DR. HURST: Excuse me. Dr. New, could we maybe just hold that until the discussion part of our Panel meeting today.

DR. NEW: Sure.

DR. HURST: Yes.

DR. PRIVITERA: I'm not sure whether you want to hold my question because it was related to the same question, but maybe there's a specific statistical question that I can ask related to that because that has to do with the slides that we saw before showed a three-month baseline and then showed the effect in the operative period of a reduction in seizure frequency after implantation in both groups. However, the one slide which was on, I don't know the slide number, but it's on page 24 of the handout, which is the month-by-month median seizure counts, is the first time I saw individual months, and it made me a little bit less convinced that the effect in the operative period was truly different than the variability in the baseline three months, and I wonder if the statistician from FDA could comment on that.

UNIDENTIFIED SPEAKER: Bottom of 23. Is that the one you mean?

DR. PRIVITERA: Yes, I'm sorry. Right, the bottom of the handout, page 23. I'm sorry. It's the slide right after that big bar graph slide that shows the responders versus non-responders.

Right, because all the previous ones that we saw showed a single value for the baseline phase. This is the first time I've seen different monthly values, and I'm wondering if you can comment on that.

MR. VAN ORDEN: I'm not going to draw any conclusions for you, but the difference between the last month of baseline and operative phase is different than when you average the three months together. So I would just say that you do have to keep in mind the month-to-month variability within the baseline phase as well, and just that's the data and let it speak for itself.

DR. HURST: Dr. Barker.

DR. BARKER: I want to ask the FDA the same questions I asked the sponsor. We're being shown a GEE analysis where the real mean of the data is in the 40s of seizure counts and the adjusted mean in the 20s, where the population experiences anywhere between 6 and 600 seizures per month, and we're being asked to interpret seizure count as the endpoint of most importance. Do you feel that that is an accurate reflection of the clinical significance of what's happening to these people, or are we just searching for the most statistically sensitive means of chasing down the tiniest little changes?

MR. VAN ORDEN: It's certainly hard to summarize all of these patients in one number, and that's just a difficulty we're going to have. I do feel like that the GEE model is appropriate. When we talk about changes in seizure counts, I would think of changes of 2 and 4 in these GEE means. The means you see in this slide as being relative to the baseline as if we could -- I mean if we could summarize all the patients in one prototypical patient, our best estimate would be someone that had 25.8 at baseline in the active group went to 19 or 17.

DR. BARKER: Given the difference between the adjusted means and the actual means, your slide showed, the one that you had to truncate because so much of the data was off the top of the slide --

MR. VAN ORDEN: Sure. Correct.

DR. BARKER: -- that seemed to show that the means were in the 40 to 60 per month?

MR. VAN ORDEN: Sure. Yeah. I mean it's a skewed population. It doesn't have a normal distribution. So not adjusting --

DR. BARKER: The difference in the seizure counts that you're telling us measure the effect, are those with regard to the actual mean or to the adjusted mean?

MR. VAN ORDEN: To the adjusted mean.

DR. PRIVITERA: In reference to the sponsor's proposal to FDA before the study, as far as the month-by-month analysis in the treatment period, so in the blinded period, because we've looked at the overall analysis and then there's this month-by-month, can you clarify for us exactly what was proposed by the sponsor before the trial in terms of the month-by-month?

MR. VAN ORDEN: It was proposed that they would test for treatment by visit interaction. So that visit has the three months of the blinded phase, shows those each separately, and that treatment by visit interaction was shown to be .06. So --

DR. PRIVITERA: Because there's a p-value that's less than .05 when just the third visit during the blinded phase is analyzed, but the proposal a priori was for treatment by visit interaction which is --

MR. VAN ORDEN: Correct.

DR. PRIVITERA: -- .069.

MR. VAN ORDEN: That accounts for some of the variability from month to month.

DR. PRIVITERA: Okay.

MR. VAN ORDEN: Like if all we had was month 3-4, then we would just look at 3-4, yeah.

DR. PAOLICCHI: I'm also going to follow up on the statistical analysis because as mentioned by many Panel members, we're trying to weigh the importance and the validity of the statistical analysis. So if you could please comment on slide number 20, the first slide, the results from the GEE model, is the answer to Dr. Barker's question in that second line? In other words, that we're validated to look at the GEE model because the log of baseline seizure counts is so statistically significant? Is that sort of the answer to the validation of the model?

MR. VAN ORDEN: It just shows that it is very important to adjust for baseline because I mean as you'd expect, people with high seizure counts would continue to have high seizure counts, and those with low would continue to have low seizure counts. So certainly not adjusting for that would be inappropriate.

DR. PAOLICCHI: If I could make one follow-up. So that point is saying that you need to look at it relative to the baseline seizure counts. It's not saying looking at the GEE model of seizure number, which is what it comes down to, is necessarily valid.

MR. VAN ORDEN: I --

DR. PAOLICCHI: I mean if I can puzzle a statistician, I should turn my microphone off.

MR. VAN ORDEN: I mean I think the FDA and sponsor agree that this is a valid analysis for a very difficult population to study, yeah.

DR. HURST: Dr. Ravina.

DR. RAVINA: I just want to comment, if you can comment on the prespecified 25 percent reduction, how that was arrived upon, if the Agency agreed to that, and if that was anchored in any, you know, previous historical precedent.

DR. COSTELLO: That was based on the pilot study experience. So it was for sample size estimation purposes only, not for actual, you know -- it was not included. We did not include that in the primary endpoint specifically that you had to have a 25 percent reduction, but it was powered based on pilot study.

DR. RAVINA: It was powered based on the pilot study, but that was thought to be clinically significant?

DR. COSTELLO: Well, the pilot studies were open label, and the sponsor was informed that this was open label data and they may wish to perform a feasibility study to actually determine the actual treatment effect in a blinded manner.

DR. NEW: Sorry. This is probably going to go back to the statistician based on the last topic. So given the wide variety and the number of seizures in the patients, is it more appropriate to look at the percent reduction in each patient on average than the absolute reduction in seizure counts?

MR. VAN ORDEN: There's certainly nothing wrong with looking at the percent reduction, and I think -- I mean if you look at the median seizure reduction relative to the median that have been presented, you can get a sense of the percent reduction.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: One more statistical question. So why was the percent reduction not looked at as one of the primary endpoints as opposed to the suggested GEE model if that may be the more clinically relevant information?

MR. VAN ORDEN: I would say it's easier to interpret. I wouldn't say it makes a better model than what we did.

DR. PRIVITERA: In a situation where a treatment or the trial design as in this case, where the control group may be getting some effectiveness, for example, in the Vagus Nerve Stimulation study, they had to give the patients stimulation in order to keep the blind. Does the FDA have specific criteria that they would use? So in other words, that they would use to try to compensate for the fact that the control group was actually getting some antiepileptic effect, for example, in this one, if there truly is an implantation effect and both groups get an implantation effect, and then there's a change from baseline, but then in stimulation, the stimulation group gets additional effect. Is there any other method or other strategies that the FDA has used in previous approvals to compensate for the fact that the control group may have some antiepileptic effect?

DR. HURST: Dr. Eydelman.

DR. EYDELMAN: I just wanted to point out that there is no currently issued guidance by FDA for these type of devices. Hence, the sponsor proposes under an IDE, the sponsor proposes a clinical trial design, and while we agree or disagree with the key safety and efficacy outcomes, it is ultimately the sponsor's trial.

DR. HURST: Dr. Barker.

DR. BARKER: Do you think that some sort of meeting to establish endpoints, this is probably not the last time anybody's going to try to build a device like this.

DR. EYDELMAN: We always aim at developing more helpful guidance documents.

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, this doesn't influence anything, but just out of curiosity, if I understand this correctly, that the study was powered based on the results of a pilot study, not taking into account the fact that the control group would also have an effect?

DR. COSTELLO: Yeah, the pilot study was strictly open label. There was no control data included in that pilot study, and I would just also like to mention that we are talking about the GEE adjusted means in median seizure reduction, but FDA did include a responder analysis as the first secondary endpoint to try to give some other meaning to whatever change was seen during the blinded phase.

DR. HURST: Other panel questions?

All right. We'll now break for lunch. We'll reconvene again in this room 45 minutes from now. Please take any personal belongings you may want at this time. The ballroom will be secured by FDA staff during the lunch break, and you'll not be allowed back in the room until we reconvene.

Panel members, please remember that there should be no discussion of the PMA during lunch amongst yourselves or with any member of the audience. Thank you.

(Whereupon, at 12:02 p.m., a luncheon recess was taken.)

A F T E R N O O N   S E S S I O N

(12:57 p.m.)

DR. HURST: I would like to call this meeting to order.

We will now proceed with the open public hearing portion of the meeting.

Prior to the meeting, one person requested to speak in the open public hearing, and we ask that when people speak in this public session, that they speak clearly into the microphone to allow the transcriptionist to provide an accurate record of the meeting. Additionally, please state your name and the nature of any financial interest that you have in this or another medical device company.

Ms. Falls will now read the opening public hearing statement.

MS. FALLS: Thank you, Dr. Hurst.

Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at an Open Public Hearing Session of the Advisory Committee meeting, FDA believes that it is important to understand the context of any individual's presentation. For this reason, FDA encourages you, the open public hearing or industry speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any financial relationships. If you choose not to address the issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Dr. Hurst.

DR. HURST: Prior to the meeting, eight people requested to speak. Again, I ask that these speakers restrict their comments to five minutes each. The first speaker is Eric Hargis from the Epilepsy Foundation.

MR. HARGIS: Hi. Good afternoon. My name is Eric Hargis. I'm the President and Chief Executive of the Epilepsy Foundation. Our organization is the national voluntary health agency that addresses both research and quality of life for the 3 million Americans who face the daily challenge of epilepsy. We are a $90 million agency with more than 50 affiliated organizations that serve communities throughout our country.

I want to make it clear that the Epilepsy Foundation has not reviewed the data on the device being considered today, nor are we expressing an opinion about it. Rather, I am here today to highlight the need for new treatment options for people with epilepsy and to emphasize that any evaluation of data must be based on treating the whole patient and not just their seizures.

The International League Against Epilepsy defines drug resistant epilepsy as, and I quote, "failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drugs." This is consistent with the Kwan/Brodie study that indicates the odds of becoming seizure free on medications once a patient has failed two drugs is about four percent. Depending on seizure type then, it is estimated that 30 to 40 percent of patients with epilepsy are drug resistant.

The more than 1 million Americans with drug resistant epilepsy desperately need new treatment options as just a single seizure can have devastating results. The unemployment rate is two and a half times the national average. There are a host of interpersonal issues resulting in an elevated divorce rate for people with uncontrolled seizures. Most frightening of all is the elevated risk of death from an accident related to the seizure or from SUDEP, sudden unexplained death from epilepsy.

But it isn't just the seizures. There are a host of comorbid conditions. Thirty percent of people with uncontrolled epilepsy are clinically depressed. In fact, studies suggest that depression or its absence is a greater predictor of quality of life than seizure frequency. There are many other cognitive and mood disorders common in people with epilepsy.

This leads me to what I hope you will focus on as you evaluate the data for this device. Please do not limit consideration to seizure frequency, but look at implications for quality of life. Unlike psychiatric conditions, epilepsy treatment can be evaluated by an easy to track metric, the number of seizures. Unfortunately, the clinical evaluation strength is perhaps also our greatest weakness in that physicians too often treat the seizures and not the whole person. A dramatic reduction in seizure frequency may be viewed as a clinical success, but if the patient has awareness or memory issues resulting in an inability to perform at work or at school, the treatment is a failure.

The American Academy of Neurology guidelines note that the seizure control profile among many first and second generation AEDs is similar and that it is the side effects that are often the key factor in deciding the right treatment option. An Epilepsy Foundation study last year indicated that three-quarters of the patients had side effects that significantly impacted a major life activity and yet most had not had a discussion with their physician about this. Not surprising, physicians indicated that most of their patients did not have problems with side effects.

So for people with drug resistant epilepsy, it isn't just about seizure reduction, although obviously that is critical. It is also about how they live day to day. Can they concentrate better at work or at school? Can they avoid uncontrolled weight gain? Are they tired all the time, or do they have the energy to enjoy their day? These are all questions that must be addressed in considering any treatment options, whether it is in the clinic today with approved treatments or an FDA Panel considering new ones.

On behalf of the Epilepsy Foundation, and the 3 million

Americans we serve, I would like to thank you for your participation in this important Advisory Council and for the opportunity to share this perspective with you.

In terms of disclosure, I have not received any compensation or considerations to be here today. The Epilepsy Foundation, while it is a $90 million organization, does receive some financial support from Cyberonics that does have a FDA-approved device. We do not receive any support from Medtronic, although the organization has in the past received grants from the Medtronic Foundation. Thank you.

DR. HURST: Thank you very much, Mr. Hargis. Dr. Dennis Spencer from Yale University.

DR. SPENCER: Thank you very much for inviting me to come here today. I really have no personal financial conflict of interest in this discussion. I am representing the American Epilepsy Society this afternoon which does receive some educational grants from a variety of industry device manufacturers and Medtronic.

I've come here representing the American Epilepsy Society, but not only that Society, but also as a practitioner in epilepsy surgery. I am Chairman of the Department of Neurosurgery at Yale but have co-directed our epilepsy surgery program for the last 30 years, an established epilepsy surgery program that sees a wide variety of very difficult to manage patients with epilepsy.

The American Epilepsy Society is a society of research and education for our epilepsy professionals. It's a very eclectic society. It has a number of individuals from neurology, neurosurgery, basic scientists, nurses, pharmacologists, and neuropsychologists. They all gather at our annual meeting for educational purposes and have close collaborations with organizations such as the Epilepsy Foundation of America, other neurology, and other neurosurgical societies.

I know that you've been over a lot of these details before. I'll give you just a few statistics, however, that will aid me in the rest of my discussion today.

First, we are focusing on new therapies for epilepsy, which is more than one seizure, often needing control by medicine and other devices, and the incidence of this devastating disorder, it's lifetime human incidence is between 1.3 and 4.4 percent with a prevalence which is most important at .68 percent.

As you've probably heard today, the mortality rate is two to threefold that of age and sex-matched normal individuals.

Although mortality is important, it is quality of life which is the essence of the destructiveness of this disorder. Individuals with continuous seizures can't drive, are underemployed, have a low socioeconomic status. They're undereducated. They often are unable to marry and, if married, are more infertile than others. It is often the accidents that lead to the morbidity and mortality, and they're often subjected to more depression and, of course, this is a very stigmatized disease.

The direct costs, those of the physicians, inpatient costs, emergency rooms, and medicines, are around $2 billion, and the total cost to society, as we know, is about $12 million.

The focus of my discussion right now will be this particular slide which will represent, using some of the statistics that I've brought to you before, the numbers of patients which we are unable to control with all of our modern drug therapy and surgical remedies.

We start with patients who have epilepsy being of that .68 percent, about 2.1 million. Most of those patients are medically controlled, about 1.3 million, but this leaves about 37 percent that you've heard before, 800,000 patients, that are refractory to multiple medications.

If we take that group of patients that are refractory to medications, they're divided into three groups. One group is the center group that are appropriate for a surgical evaluation. So they're not controlled with medicine, and they may be evaluated for a possible surgical resection of an area of the brain that is responsible for the seizures, and its resection will not cause neurological or cognitive harm. Unfortunately about 23 percent of these patients are not suitable for evaluation. Even more unfortunate is about 260,000 patients that are never referred in the first place.

Of those patients that are evaluated, it divides into a 50/50 split. Those patients have a MR abnormality that correlates with electrophysiology and behavior to lead them to a resection. The other individuals that do not have a correlative workup often go to an intracranial study using depth electrodes, grids and strips, and that again is about 50 percent or 180,000 individuals.

Of those patients who are resected, certainly not everybody is controlled. At least 30 percent of patients continue to be refractory after resection. Of those patients studied with intracranial electrodes, about 24 percent are not even subjected to resection, but those that are resected, these are usually MRI negative, neocortical epilepsies, those are resected, being about 76 percent. Unfortunately, only about 30 percent of those can be controlled.

So this means that about 1.5 million of the original 2.1 million patients can be controlled with our present day medication and surgical procedures, but there's a large group then of individuals who are the worst of the worst patients, the most refractory, representing about 630,000 individuals that are not controlled.

As we know, and you've heard today, and I won't go into this slide at all, it just repeats the evaluation for the SANTE study as I took away from our American Epilepsy Society meeting this last December and, you know, the details for inclusion and exclusion criteria for the study is just that from that meeting it appeared that at least in the long term, both the blinded and unblinded portion of this, that the efficacy of brain stimulation, thalamic stimulation for epilepsy was at least as efficacious as other devices which are both FDA approved and not yet FDA approved.

I will not go over these cases. They're in the handout that you have. I've included them in the handout because they represent patients at Yale that are actively, just a handful, a sample of patients at Yale that are waiting for some possible new therapeutic device because they are unmanageable by medicine and surgery at the present time.

Anecdotally, after listening to the end of your conversation this morning, we do a lot of intracranial electrode study at the Yale program, and over the years that I've been at Yale, at least, you know, six to eight patients have been controlled by just putting electrodes in, and we have had one patient, because we do study the thalamus, when we do place our electrodes, for intracranial study, we often put an electrode in the thalamus to look at spread patterns, and we've had one patient who without a hemorrhage, just with the electrode, did not have seizures following implantation.

So, in conclusion, there are a substantial number of patients who suffer from epilepsy and are refractory to all available medical and surgical treatments. And the anterior nucleus of the thalamus stimulation seems to be an effective treatment, will be valuable in so many of these patients that are uncontrolled at the present time, and the bottom line is that these cases are very complex. There are very many substrates that result in intractable epilepsy, and it is essential for neurologists and neurosurgeons treating these patients to have a variety of therapeutic approaches so that we can use clinical judgment in making decisions about what may be the best. Thank you very much.

DR. HURST: Thank you, Dr. Spencer. We'd now like to hear from Troy and Jenny Gibson.

MR. GIBSON: Hello. My name is Troy Gibson. I am a patient and a participant in the SANTE study and was invited here by Medtronic. I am the one who was the outlier in the study who experienced for one day an increase in seizures.

I am from a small town in Northern Wisconsin, with my wife and three boys, where we run a family resort together which has been a challenge to do with epilepsy. I developed epilepsy as a child when I was bitten by a mosquito carrying encephalitis. During my early 20s until I tried the deep brain stimulator four years ago, my seizures got worse and worse. They went from mildly annoying, petit mals that most people did not even notice, to complex partials where I was falling on the ground and sometimes getting injured.

Before trying the deep brain stimulator, I had taken many different drugs. The drugs controlled some of the seizures but never completely. All the drugs made me feel tired and worn out. The worst, Trileptal, had the side effect of making me cross-eyed, have double vision, and dizzy. This led to a few rumors around the resort from the guests that I was drinking in the morning.

The tradeoff, only partially controlled seizures, and all the side effects made the quality of my life not what I'd like. In a frustrated way, I felt that these 24 hours a day, 7 days a week side effects of these drugs were harder to deal with than a 3 minute complex partial and a 30 minute recovery, for which if one sneaks by me now, coming back together is much quicker.

Not only were the effects of these drugs an influence on my reasoning to try the stimulator, but I considered myself socially impaired. The past 15 years I have felt a bit of a social misfit. In the back of my mind, I always had a fear of wondering when and where would my next embarrassing moment occur.

I think at times I hid from the world. I will admit that I am a bit of a quiet person, but these episodes made it harder yet. Many times I would be asked by the guests, saying come on over with us to somewhere; my usual response would be thanks, but I've got something to do, I've got some work to do.

When Dr. Sandok of the Marshfield Clinic approached me about the deep brain stimulator four years ago, I felt hope about the possibilities. I questioned myself on whether I really wanted two holes drilled in my head while I was awake and a battery installed in my chest. To me, it was not a difficult decision to make after all I had been through with seizures and drugs.

I wanted to enjoy my life and be able to participate in my boys' lives more. My goal in having DBS installed was to get better control of my seizures and reduce medications as much as possible.

The benefits I have experienced in having the DBS stimulator installed have been nothing but positive. Before the DBS stimulator, I tried to coach my son's third grade basketball team, something every dad wants to do for their son. During one of the games, I had a seizure, falling to the floor and disrupting the game and causing quite a disturbance. I gave up coaching after that embarrassment.

Since having the DBS, I now have enough control of my seizures that two weeks ago, I felt comfortable to run the time and the scoreboard in his ninth grade game.

Also, I'm having a better relationship with our guests at the resort, being invited to horseshoe tournaments and evening cookouts. The DBS has allowed me to be more comfortable and confident to do something in a public environment.

My seizures are not 100 percent controlled with DBS, but the control I have been given by the DBS has made a difference in my life and my kids' lives.

In my work of running a family resort in Northern Wisconsin, I am constantly being called on to do work that for someone with epilepsy is a challenge. Putting docks in during the spring, running power tools, climbing ladders, my wife's favorite, going on roofs of cabins to do maintenance. Since getting better control of my seizures from the DBS stimulator, all of these things have become easier for me to do and safer.

The stimulator for me has not been the magic bullet I hoped for, taking away seizures 100 percent. It has improved my control of my seizures by reducing the number and intensity of the seizures. I am slowly right now reducing the number of drugs I am taking and still see no increase in seizures.

Having the control to activate the stimulator when I feel a seizure coming on has helped me to stop some of them from developing into a full complex partial seizure.

Through reduction of drugs and being able to have the controller, I feel that I am in better control of my life. To me this has improved my life with my family and allowed me to enjoy it more without fearing so much, what if I have a seizure?

I do not regret in any way having this procedure done and am happy to have participated in the SANTE study.

MS. GIBSON: Hello. My name is Jennifer Gibson, and Medtronic has made it possible for me to be here to represent the silent folks in this room who are affected by epilepsy. I do not have epilepsy, but my husband does, and I have been just as affected in my life by the benefits of the DBS as he has. I am the one who has watched helpless over the past 20 years as I see the blank look that comes over his face at the beginning of a seizure. I am the one that makes sure that he is in a safe place while the seizure is going on. I am the one that explains to folks around us that he is not drunk or having a heart attack. I am the one that figures out how to turn the water off to the toilet that he fell into when having a seizure and knocked it off the foundation spurting water. I am the one explaining to our three boys why he can't go downhill skiing because the chair lift is not safe for dad.

I can, without a doubt, say that the DBS system has affected our lives in a positive manner. Before the DBS implant, we were becoming more and more frustrated. The drugs were losing their effect. The seizures were increasing, and the side effects from the drugs were making life difficult.

Try having 3 boys and run a family resort with 11 cabins when your spouse is exhausted from drugs and is having frequent seizures. It's a marathon of multitasking and trying to be in too many places at one time.

His seizures were getting to the point that they were strong, complex partials and caused him to fall over. We both had concerns with me leaving him alone with the boys when they were babies. What if he dropped them or was unconscious?

Through the years I saw him become more and more restricted in what he could do in life. When we met in 1988, Troy could drive a car and enjoy life with his college buddies, just like any other normal college guy at the time. He was just having small petit mals.

By the time we were looking into the DBS, he had been giving up driving and was avoiding social situations in fear of what if he made a fool of himself by having a seizure in public?

You question everything. Is it safe to go swimming with the boys? What if he has a seizure in the lake and they can't help him or I am distracted talking to someone and do not see him starting to have a seizure? This is the dilemma that faces anyone with epilepsy and those of us that live with them.

How much do you restrict your life to stay safe? Imagine you had epilepsy and had to give up driving, to be driven everywhere by your spouse. Imagine telling your kids you can't coach their basketball team or go on a field trip because you may have a seizure, and you start to see the restrictions epilepsy puts on a person and those that live with them.

These reasons are why we agreed to take a risk with the DBS. Since the DBS was implanted, I have seen his life change in small ways that for us make life easier and more enjoyable to live. Because the DBS did not give him 100 percent control, some things we cannot change, and we face those, like he will never ever drive a car again, and chair lifts for downhill skiing are still out.

The benefit I have seen from DBS is the reduction of seizures and the severity of the seizures. These two things have made our lives with three boys and a family business manageable. I do not get a knot in my belly when leaving the house to go on an errand as much as I used to.

We live on a lake in Northern Wisconsin, and I used to dread when the ice went out on the lake. Ice out for me meant danger when he was falling over with seizures before DBS.

Now, with DBS his seizures, when he has them, are mild enough that they either pass off quickly or he just stands in one place confused for a few minutes. The DBS has given us some of our freedoms back. I know most people in this room are scientists and doctors, and you look at charts and numbers. I know most of you look and say his result was not 100 percent control. Believe me, I wish he was the one with the 100 percent control, but the results I have seen and our kids have seen has given us some normalcy to our lives. Our boys may have to live with not going downhill skiing with their dad, but they will be the first ones to say, we have been able to do more things since DBS, even if it's cross-country skiing instead of downhill.

We even managed a trip to the Grand Canyon a few years ago. The Grand Canyon is a mom's nightmare. It needs more guardrails, and it could benefit from some of those stimulus dollars. It is scary to take kids, let alone having a spouse who falls with seizures. We felt comfortable enough to take walks and enjoy the Canyon, even with the lack of guardrails, because he had better control of his seizures. We did not take the hike down in the Canyon, but with DBS we got to enjoy a family trip that was once in a lifetime and we would not have taken before the DBS surgery.

I'd like to thank Dr. Sandok, the Marshfield Clinic, and Medtronic for giving us this opportunity to participate in the DBS study and hope the FDA offers that opportunity to more people who are in our situation with uncontrolled seizures.

My husband is the one that caused all the stir this morning being the outlier and person A in the study, Subject A. I was there for the 24-hour period of small seizures, and believe me, that is a minor thing in our lives, and we laugh about it today and would not change a thing. Thank you.

(Applause.)

DR. HURST: Thank you, Mr. and Mrs. Gibson. Next, we'd like to hear from Shannon Bagy and Jacqueline Miller.

MS. BAGY: My name is Shannon Bagy, and I'm a patient. I'm also a participant in the SANTE clinical trial. Medtronic has made it possible for me to be here today.

DBS has brought me one step closer to living a normal life. In February 2002, I was diagnosed with encephalitis. Before encephalitis, I was a full-time college student going for a degree in elementary education with a GPA of 3.7. I worked part-time at a daycare and had an active social life.

Due to encephalitis, a typical week was three to four severe grand mal seizures. During the seizures, I would shake tremendously, bite up my mouth and tongue to a point of vast amounts of blood, and at times stopped breathing. After a seizure, it would take me about two days to recover where I would sleep most of this time.

The seizures caused short-term memory loss. I would not be able to tell you what happened the week before and at times the day before. This made conversation a bit confusing for me.

I had a hard time processing information. Therefore, I could no longer read, which was a great hobby of mine. I could not grasp and follow through with simple tasks. I was no longer able to drive, and my social life was lost because I no longer felt comfortable going out in public for fear of what would happen if I had a seizure and the embarrassment it would cause. This caused me to grow apart from many of my friends.

Unfortunately, this was all happening when I was supposed to be taking my final teaching licensing exam. This was the last exam which would grant me my teaching license and enable me to teach. Since I was having a difficult time grasping and retaining information, I was unable to pass the exam.

I was angry and depressed. I couldn't understand why this had to happen to me. I went from a typical 20-year-old to an angry upset 22-year-old. I was scared because I had no idea what I was going to do with my life and if I was always going to have to depend on others. I no longer had any goals, and my days consisted of watching television.

About a year went by when I was offered the opportunity for the deep brain stimulator trial or DBS. The DBS had hopes of controlling my seizures and maybe ridding me of them completely. There was no guarantees, but it was still hope. I accepted this opportunity because to me nothing could be worse than the life I was living.

On September 22, 2004, DBS was implanted inside of me. It took a gradual amount of time for the DBS to reach the effect it has now, and the device needs to be programmed to you and what works best with your body and your seizures.

My seizures have now decreased in number and severity. I now have about one to three seizures a month. I no longer bite at my mouth, stop breathing, or feel sick after a seizure. About 95 percent of my seizures now take place at night, and if I do happen to have one during the day, I may feel a bit tired and, if possible, take a short nap.

Since DBS, I went back to school and took a couple of education classes where I received A's and B's. Most importantly, I was able to pass my teaching licensing exam and achieved that goal I had set for myself.

I now have a license to teach. Though I will probably never teach, I felt great pride and tremendous happiness that I was able to accomplish this goal.

Though I do still have seizures, since they have decreased in severity and number, I feel I am back to a normal mindset, maybe not as great as before the encephalitis, but so much better than before the DBS during my seizure period. I am now able to comprehend so much more.

Though I am still unable to drive or have a job, it is said that I may be able to have a job sometime in the near future. I can now go out with friends without fear of having a seizure in public. I love to read and do so a lot. I can now comprehend and retain information from the books. I can now complete and follow through tasks. I help out my friend by baby-sitting her two children when she needs me.

I also volunteered and taught Junior Achievement to school-age children.

I have a great passion for animals and love to take care of my two dogs. Over the past two weeks, I have put in an application to volunteer at the animal shelter. If I enjoy this, I plan to take some online classes to become a veterinary technician.

It's weird. Most people get annoyed at the fact that they have to get up and go to work every morning. This is what I truly want to do. Because of DBS, I feel I am now in the mindset to do so soon. I have hopes of becoming a veterinary technician. I have hopes to someday get married, which is something I would have never said before.

I may not be completely rid of my seizures, but my frame of mind is so much better than before the DBS. I now have goals for life, and I am not afraid to set forth and achieve these goals. I am one step closer to living that normal life, something that has been a longtime struggle for me.

I won't ever be what I was before the epilepsy, but the DBS has brought me so much closer to living that normal life, the normal life that so many people take for granted. Thank you.

MS. MILLER: I'm Jackie Miller. I'm Shannon's mom. I'm also a registered nurse. My normal field of work is quality management. So I kind of know about those numbers you were talking about this morning.

I have no financial affiliation with Medtronic, other than they made it possible for us to be here today.

From my perspective, the deep brain stimulator has given Shannon hope, hope of a normal life. To me the deep brain stimulator has given me my daughter back.

When Shannon was diagnosed with the epilepsy, her life was put on hold. Her friends finished school, married, had children, got a job. Shannon stayed in just that post-epilepsy period where her day consisted of watching TV and waiting on the next seizure.

Now, she actually has plans for her future. As she said, life before epilepsy, typical college student, good grades, grades came easily. That all did change in February of 2002.

As a mom, I watched my daughter's seizures increase. I had to call a code on my daughter. She was in a drug-induced coma. She had two years worth of memory loss. So when she did go back to school, it was a challenge. Initially, after rehab, her seizures were somewhat controlled for a period of a few months, and she did return to school and graduate, but learning wasn't the same. It was a challenge. Shannon maybe could pass a test, but she could never apply that information.

When I talk about her general or grand mal seizures, they were nasty. Stopped breathing, turned blue type, and as a mom and as a nurse, I was helpless. All I could try to do was keep her safe and say, breathe, Shannon, breathe.

After these seizures, the recovery period was anywhere from 10 to 30 minutes just for her to get oriented, 24 to 36 hours for her to get back to her baseline.

As the seizures increased, Shannon's life continued to deteriorate. At 23 she couldn't drive, couldn't remember last week. She was asked not to return to a part-time park job because she couldn't make change. I told my husband, you know, if we had to go away, we had to try to make arrangements to have somebody drop by or call. A 23-year-old doesn't want a baby-sitter.

Shannon had great defense mechanisms. In a weak moment, she told me, I just want to be normal. It broke my heart. She was devastated when she finally figured out something that we had seen happening over time. She was losing her memory. She couldn't remember. She'd see a movie up to three times, and her friends were great. They'd go along and see it again. She didn't want to be dependent on us, but she was really afraid for her future.

Shannon couldn't think through simple processes. If she used her credit card, it didn't always translate to paying her bill. If she couldn't get the e-mail on the Internet to work, she didn't think to check the connection.

We were desperate. I just felt that if we didn't do something, Shannon was going to die. She was just going to not start breathing again after one of her really bad seizures. Our local neurologist tried numerous drugs and drug combinations. It caused her to get fat, lose her hair, get skinny, memory loss. So we were referred back to IU and admitted into the trial.

After surgery, over a period of months, the severity of the seizures greatly diminished. Now, she recovers from a grand mal seizure, she's reoriented within 10 minutes, and she loses a couple of hours and maybe has to take a nap. She usually has 1 to 2 seizures a month now compared to 8 to 13, and when she does have an extra seizure, it's because she's fragile. If she misses a medication dose, I know it's theoretically impossible, but she'll have a seizure within 12 hours.

She also needs her sleep, and if she doesn't get her sleep, she has a better chance of seizures. The one thing when I was listening to you this morning that I didn't feel was taken into consideration is she may have more seizures on occasions, that third one a month, but it's because she's living her life, and she wasn't doing that before this trial.

So it had a big impact on our family. We now are all moving on and making plans for our future. We are so very fortunate to have been able to participate in this study. I feel guilty because there was so many people with epilepsy, but we were given the chance to have Shannon's life back, and I really feel like as a family, we're moving on. Thank you.

(Applause.)

DR. HURST: Thank you very much. Next we'd like to hear from Tina Nichols and Tethia Longworth (ph.).

MS. NICHOLS: Hi, my name is Tina Nichols, and I'm a patient and participant in the SANTE clinical trial. Medtronic made is possible for me to be here today.

I was diagnosed with epilepsy over 24 years ago, and still to this day, we don't actually know why. When I was still in high school, we got the diagnosis, and then when I went on to college, my life became much less about books and studying and more about being controlled by epilepsy. Thanks to this deep brain stimulator, I now have control back over my life.

I definitely lost jobs because of seizures. I stopped driving several years ago after having my third wreck because of the seizures. I had to move back in with my parents because of seizures. Epilepsy had taken away all of my independence.

I was afraid to be alone with my niece and my two nephews because I didn't want to have a seizure around them and either scare them or, even worse, hurt them. I didn't socialize or have many friends because, you know, what if I had the seizure in public and again hurt somebody or, you know, embarrassed myself.

I had been on many different medicines for the treatment of my seizures. Some worked better than others. However, none of the medicines actually controlled my seizures fully.

I was extremely depressed and very withdrawn. I didn't feel like I had any hope of living a normal life. I've even gone through some presurgical testing for a temporal lobectomy, and that didn't work out either. Basically it was determined that that surgery could do more harm than good for me.

I finally got a glimpse of hope almost six years ago when my neurologist told me about the SANTE study and the deep brain stimulator. I was definitely willing to participate in this trial, and I have no regrets about my choice. The deep brain stimulator has definitely changed my life for the better.

I still have seizures. I know that I probably always will, but on average, I only have one seizure a month now. The seizures don't last as long, and it doesn't take me as long to recover from a seizure. I started working again part-time, and I've had the same job for two years now. I've been able to move out on my own again and have lived on my own for almost three years. Even though I will never drive again, I know that I can get around by myself now because I can use the public transportation system in our city. It doesn't scare me anymore, and I can get wherever I need to go. Being out in public doesn't scare me. I interact with people all the time at my job, and I actually enjoy it now.

I'm also in a very active and socially active singles group at my church. I've made many new friends there, all very understanding, good people, and not having as many seizures and not having to worry about having seizures has made me more confident, and even when I do have a seizure, I know now it's not that I've done something wrong that's made me have a seizure. I know that I have a serious disease that at one time took over my life, but now thanks to the deep brain stimulator, I have my life back, and I hope that the deep brain stimulator will be approved because there are many people I know out there with epilepsy that are going through the very same thing that I went through. Thank you, and I would like to introduce my mom, Tethia Longworth.

MS. LONGWORTH: I am Tina's mom, and I came here at the invitation of Medtronic, and I'm extremely happy that we are talking about treatment and research for epilepsy, obviously a condition that so profoundly affects our lives.

One of the benefits, and I think one of the number one benefits for Tina, of the deep brain stimulator, is just being able to regain her self-confidence and her sense of hope. Before the deep brain stimulator, she would not have been able to be here talking to you and sharing her life experience with you physically and mentally. She just would have not been able to do that.

Epilepsy had progressively taken over her life. She went from having a normal childhood and being a normal active healthy teen to a person with seizures that began to get more frequent, more severe. She's had to endure rudeness and rejection and misunderstanding from the time she was in high school, parents on the same athletic team she was on, to employers who thought that she was on drugs or being lazy or whatever other misunderstanding they might have had.

She's lost her independence as she said, had to move back home again. The last thing you want to do when you're 16 is lose your driver's license when all your friends are beginning to do that.

She became increasingly isolated. She basically became unable to function just in everyday life because having a seizure would not only impact her for that time, but for several days afterwards. Depressed, and constantly that worry hanging over her head. As a parent and a family member trying to provide support, that's your biggest gift to them because you cannot do anything else to get rid of the seizures.

But truly, truly, I had my reservations about trying something so radically different as this procedure, but I have absolutely nothing but positive things to say about it. Since the DBS began to reduce the seizures, gradually

Tina began to regain control of her life. She's able to do things that each one of us do on a daily basis and take for granted. She is much more self-confident and hopeful and able to contribute again to life.

I think that, you know, I'm proud of Tina and each person that lives with epilepsy, just because they have to face every day with courage, and I'm especially proud that she was willing to try the deep brain stimulator. It was a risky thing, but she was willing to do it not only to try to help herself but to try to help other people who have epilepsy, and we've seen such positive results that I just, you know, want to voice my opinion, that it's so important that we go ahead and make this available to other people with epilepsy who do need it. Thank you.

(Applause.)

DR. HURST: Thank you very much. Is there anyone else who would like to speak at this time?

All right. Since no one has come forward, I now pronounce the open public hearing to be officially closed, and we'll proceed with today's agenda.

We'll now begin the Panel discussion portion of the meeting. Although this portion is open to public observers, public attendees may not participate except at the specific request of the Panel Chair. If you're asked to comment, we remind you to identify yourself each and every time you speak. This assists the transcriber in identifying the speakers. And I think we'll begin with the general discussion. After 30 minutes or so, I'd like to focus in and begin to get a sense of the Panel's understanding and concerns regarding the questions that we're going to have to formally address in the next hour since these are going to aid us in coming to a decision regarding the disposition of the PMA.

We might just begin our general discussion with Dr. New and some of the issues that he began to raise earlier this morning.

DR. NEW: I think I made my feeling about that one aspect fairly clear. I think it's a shame in a sense that a lot of the debate statistically this morning is about whether there's a benefit of just the device being turned on versus being placed alone. And I'm not trying to -- obviously the study's done. We can't rewrite it, redo it, but my point about that really is that following the patients in the unblinded phase of the study showed a pretty significant reduction in the percentage of seizures in patients with the device implanted, and I understand the limitations of being a non-blinded part of the trial, but also one of the benefits I just felt like hadn't been expressed really that clearly by either side was that unblinded part and in the long-term follow-up most closely mimicked how the device is going to be used and do take into account both the positive benefit of placing the actual physical device, which does apparently have some small leaching effect, as well as turning the device on.

And I don't look at it as a negative in the long-term follow-up that patients were able to have their medications changed. I mean, I think in reality when this device is on the market, that's how it's going to be used.

DR. HURST: Dr. Evans.

DR. EVANS: So I have one comment about that. I'd like to make two comments, and I'll come back to yours as a second one.

Let me first thank the sponsor and the FDA for their presentations. I realize the complexities of these challenging issues, and I appreciate your efforts in trying to understand the data. We all want to be right.

Prespecification of an analysis strategy is a fundamental practice in clinical trials and with good reason. It prevents researchers from conducting many analyses and then selective reporting the most desirable result.

In this case, GEE, generalized estimating equations, is a modeling strategy that was preplanned or prespecified for this particular trial, and it's a very common strategy for analyzing repeated measures data as done in this trial.

Now, some very good model diagnostics that were performed showed that there's one or two participants in the trial that had very influential observations that contribute or give a lot of influence to the parameter results that come out of the GEE model.

So that leads us to, we get put into a situation where the qualitative result of this trial rests on whether we include a single patient or not, and so we came to the issue about whether that patient should be excluded, and we come to the intent-to-treat principle. The intent-to-treat principle says you analyze people as they are randomized, and you don't throw out anybody. And there are a couple of different reasons for that.

One is if you start throwing people out, you worry about the generalizability of your result because you're now selectively analyzing people and are not quite clear about what the results generalize to.

The second reason is a statistical one, in that randomization is the foundation for statistical imprints. It's the statistical tool that allows you, that provides the statistical foundation for calculating p-values and calculating confidence intervals. Without that randomization and intent-to-treat principle, you've lost that foundation. You haven't analyzed people as they were randomized. And also that randomization gives you the expectation that when you start to compare groups, you have the expectation of balance of both known factors but also unknown factors that are beyond our comprehension at this time and beyond things that we can measure. And if you don't adhere to that intent-to-treat principle and to randomization, you can lose that balance.

But we also realize that there are cases, such as this one, where individual patients have undue influence on the outcome of the analysis result.

I think Dr. Barker made a statement earlier today that was very interesting, and I think it was a very good question. He asked are we doing the right analysis?

Now, we all want the result of this, the outcome of this, to be robust, and right now it's riding on the effect of one patient. It's not very robust. Okay.

Now, I could propose there are issues with GEE modeling. GEE as I mentioned, is a very sound strategy. This is a very common strategy to analyze trials, but at the same time, none of us want to bet the house on a result that seems to be contingent upon the outcome of one patient. So the question is, is there a more robust strategy for analysis that could give us a result we're all comfortable with, and I'll make a proposal in a minute.

Now, let me just mention that we interpreted the two results of this trial, and when I say two results, one with the inclusion of this patient that we met earlier and one without. Now, in one particular case, we had a significant p-value, and in another case we don't get a significant p-value.

Well, let me just first clarify, p-values are a composite statistic. They're a function of sample size. They're a function of variation. They're a function of effect size. We often interpret them as meaning something about effect size.

So I think it's very important for us to not only look at the p-value, but the magnitude of the effect, the clinical effect, and there was some very nice summaries about that.

A high p-value does not prove there's no effect. A low p-value does not prove there is one. Okay. They are statistical tools that we use to help us understand the data. All right.

Now, some of the problems that have been proposed is we have this influential, this one patient whose data is very, very influential in the analysis, an extreme observation, and we also have the question of whether we're jeopardizing the integrity of the trial by potentially deleting patients, or deleting this particular patient from the analysis, in violation of ITT, a strict adherence rule of ITT.

We also have a potential issue of multiplicity when we start looking at multiple time points and modeling strategies in which we're selecting and deselecting variables that go into the model. We begin to run into some statistical multiplicity issues that we have to be concerned about.

So perhaps I could ask both the sponsor and the FDA to comment on an idea, an idea that hopefully would give us a more robust results, one that doesn't hinge on one patient. Frankly, it's a very difficult position to be in, that we're all in here today making a decision based on the result of one patient.

So let's think about the outcome variable for patients in this trial. At three different time points, you collected the number of seizures that each patient had, and because you did this at three different time points, you've got multiple observations on a person, but those three time points are just asking for or collecting the number of seizures for a particular patient. What's so special about those time points? In other words, during the entire span of say the blinded phase, you're just counting up number of seizures. Essentially you could get a summary count, a single count, for any particular patient, eliminating the need for any GEE at all.

Number two, you have the problem of extreme value, an extreme value. Could we do something rank based? What that means is that you compare treatments with respect to ranks rather than allowing some extreme value to pull up means and medians. Could we look at something non-parametric, something rank based?

Adhere to the ITT principle, include everybody. You don't have to toss out people because you're going to do rank-based stuff. It's more robust to extreme observations and avoids the time point multiplicity issue.

Now, there was some discussion earlier today about the baseline variables that are potentially significant in some model, and you can include those or not include those. You have a randomized trial. You get a valid estimate of treatment effect whether you include those guys or not. Now, occasionally you can do a little bit better by including them, but let's be clear. When you put baseline in a model, baseline was a significant predictor of outcome. That does not mean that baseline affects the treatment effect on outcome. That's a different question, and you're interested in treatment effect.

Okay. So with randomized ITT clinical trials, you can go with or without baseline covariates in your model. If you want to include them in, that's fine.

Now, let me just make one last comment about Dr. New's comment. There's been a lot of talk today about the "effects of the device," but there's a lack of clarity on what that means.

Now, one definition of what that means is the effect of stimulation and that we can directly measure in this trial using the blinded phase. We've got a control group. So we can measure the effect of stimulation. We have that.

Another question is what's the effect of implanting the device plus the stimulation? That's a different effect. Now, we don't have direct data in this trial to answer that question. Effects are measured by a contrast to their count of actual in order to estimate that effect. You would have to have a control group who had no implant, no stimulation. We don't have that in this trial.

Now, we could say that we can estimate that by just change over time. That, of course, assumes that there's no natural history effect or placebo effect going on, all right. So under an assumption, we can estimate that effect, but we can't measure it directly.

You could always compare it to historical data if we have it, or base your judgment on whether that change is significant or what have you, on clinical experience but, of course, you're subject to all of the potential biases of historical data and epidemiological evaluation.

So I think as discussions proceed, I think it's important to realize which effect we're talking about because there was a mixture in some of the presentations.

DR. HURST: Thanks, Dr. Evans. Dr. Engel.

DR. ENGEL: I'm really pleased to hear a statistician talk about how things might be a little different and that we're not going to necessarily rigidly adhere to the way things were originally set up.

But I wanted to comment on the effect of the surgery because it looks to me like the effect of implanting the device and stimulating was as predicted from the pilot study. What was not the same was the effect of the control group, and it's well known that any kind of surgery causes a reduction in seizures that's transient.

At the beginning of the 20th century, people were doing all kinds of non-brain surgery as a treatment for epilepsy. In fact, Wilder Penfield's first paper on epilepsy surgery was on thymectomy, and so people did thymectomy and appendectomies for epilepsy because it made seizures go down, but it was transient. It lasted a few months, and that's exactly what we've seen in the control group is that it went down for a couple of weeks and then it started to go back up again and probably eventually would go up to baseline. So I wonder what can be done about that if you just accept the last month of the blinded study. I think there's clearly a trajectory there.

DR. HURST: Other comments? Why don't we just begin and work our way around and if anyone has any comments. Dr. Nikhar, any general discussion on the issue? And then we can move in to begin to address some of the FDA questions.

DR. NIKHAR: You know, there's been a lot of discussion about the efficacy, and in terms of a lot of this discussion has been based on statistical findings. And as I heard both presentations, I felt that there was much made about the fourth month data or the one month data and the last part of the blinded or the last blinded month. And then the discussion went on to the seizure reduction between the two groups.

It would be nice to know what the actual seizure reduction was during the unblinded phase. I'm sure the data's there somewhere if it's been analyzed month-to-month because in the graph that we saw, though there was a general decline in the number of seizures, the difference between the two groups seemed to be quite similar in the graph, going up to I think the 14th month.

So again that sort of roll balls into this actual stimulation versus the creation of the lesion effect, and I didn't get the sense that there was a persistent difference which would seem included as 40 percent in the 4th month, whether that difference was actually maintained throughout the unblinded phase.

DR. HURST: What would you think about that magnitude of difference, Dr. Engel? The effect, in other words, the fact that you did get a drop in both of them, however, the control group began to come back up, you feel that that would be exactly what would be expected?

DR. ENGEL: Yeah, they were stimulated after the fourth month. So they had the effect of the stimulation. But what you saw, if you look at the curve, is between month 3 and 4, the control group went up, and as soon as they started getting stimulated, they went down again.

DR. HURST: Because I think that's a very important aspect that a number of us have paid quite a bit of attention to, that both groups initially went down, and I think that that's a very important aspect of behavior in people who do have surgery that do have seizure disorders. Dr. Privitera.

DR. PRIVITERA: I find this a very challenging situation to be in because I would agree, I think my basic feeling is that there may be some type, as we've spoken, some type of an initial effect, although as I mentioned with that graph, with the individual monthly seizures, my impression looking at the three-month baseline seizure frequency compared to the operative month, before stimulation started, looks different, although statistically that was not measured, but when you look at individual months, I'm less convinced that there's really much difference there although I wish that we had some type of a trial design that could eliminate this idea that there's an effect of implantation plus an effect of stimulation because as everybody knows, what we really measured here was a difference between stimulation and no stimulation and not really implanting the device.

I think it's a difficult place to be because I think statistically the way the trial was designed, the data that's been presented to us, we can't really determine whether that effect is truly there or not.

I think on the other end, when we look at the long-term data, the long-term data do have some positive trends that do look fairly impressive, although it is open label data and, you know, certainly in the long-term data, there's medication changes. There's certain placebo effects. There's all those other effects that we're not controlling for.

So when we really get down to it, what we really need to do is to look at that treatment phase and look at the control group and the active group.

And then I think the question really comes down to this outlier effect, and what do we do with an outlier? If you eliminate one outlier, then the FDA's position is that you probably should eliminate Subject B, who was another outlier for a totally different reason.

So I would be much happier if the data that we were given had better outcomes in some of the secondary variables. I'm a little disappointed that if we're going to look at data where we're saying that one patient is really making the difference between statistical significance and not, that I would feel much more comfortable not saying that I don't, you know, I'm not making any decision yet, but I would feel more comfortable if some of the secondary variables were a little bit more positive, that if the sponsor could come to us and say, gee, you know, we had all these variables to choose among, we chose this variable, and yet it wasn't statistically significant, but we've got these other variables that we didn't chose as the primary, and some of them were statistically significant.

So I think it would be an easier decision if we had much stronger results in some of the secondary outcomes to be able to say, yes, we can drop this outlier and then really say that we could make a change in our a priori plan.

So I think that this will require a lot of deliberation and some significant judgment on our part that I think is not going to be just simply statistical nor simply clinical.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: We looked at so much data, so much of the long-term data, and that also influences the way you look at the other data, and when you look at the difference in the active versus control portion, the controls were not having as much difficulty it seemed with depression, memory, their quality of life scores were a little different, and it almost asks this other question that in clinical practice, would there be patients who have been very seriously troubled by depression or memory problems for whom the treatment strategy might look better, like the controls who waited to get turned on, and whether or not that ultimately would be something that would be studied in postmarketing assessment, that the control group eventually got the advantage of getting the stimulation, and they weren't studied exactly the same way as they were in the randomization group, but there were those differences in some of the non-seizure-related aspects.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: This group represents over two decades of disruption before being entered into the trial, and expecting that there's going to be significant change within one, two or three years, neurobehavioral, is quite a remarkable expectation since they spent over two decades with a disrupted psychosocial, cognitive storm. I think we have to ask ourselves what are we really expecting from this group?

The outlier represents a likely patient seen in the clinic over a long period of time. This is the real world. We're going to have outliers. I'm not exactly sure. I don't have the answer as to how to handle the outlier, but I think we all respect that there are going to be outliers.

I might make a comment or two about the methodology, at least the neurobehavioral methodology. There have been a series of repeated measures. Take a look at memory, quality of life, over the study period, and exposing the sample, the subjects, to six or seven repeated measures as I count and then moving forward perhaps more.

The retesting of these folks with the same measures introduces a variety of other concerns, and presumably the sponsor's consultant took this into consideration and is using alternative methods or alternative procedures, alternative forms, in the cognitive testing to help explain the retest issue.

Also over time, with testing, we tend to see a regression toward a mean. If we sample people repeatedly, you're going to see an average performance, and are we being distracted with statistics because of this average weighted performance over time.

We're also seeing some greater variation in some of these cognitive domains. The standard deviation increases. We get that with repeated measures.

So from my perspective, I don't see any surprises at least from a neurocognitive point of view, and I see a study population that has been disrupted for a long time, and it's difficult to expect that they're going to turn around within several years.

DR. HURST: Thanks, Dr. Petrucci. Dr. Good.

DR. GOOD: Well, I certainly realize as we all do that this is a very severely affected population, that we need more treatments for epilepsy, and certainly that was brought out in the public discussion. There's no question about it.

The issue of the outlier I'm going to have to throw to the statisticians. I'm not a statistician, but my concern about throwing it out is it seems pretty clear that other people had seizures when the device was turned on, too. So to throw out one individual where we know a number of others had the same problem, statistically it just doesn't make me feel good.

The other thing that hasn't really been brought up in the discussion so far is how the long-term follow-up information should be handled. You know, as presented by the sponsor, it looks good.

On the other hand, there were a lot of dropouts. They did a good job in trying to explain the dropouts by looking at the worst case scenarios, and by imputing based on their previous seizure frequency going forward, and when one looks at that, it seems to blunt that concern a bit. But, again, it's observational. There were multiple changes in medications long-term and multiple changes in the stimulus parameters. That was one thing that was new that the FDA brought up were these different stimulus parameters that were used, which, of course, brings another whole variable to the table. And so it makes it difficult to evaluate these long-term open label patients. It's clear a lot of people did well, and it's wonderful that six or eight patients were seizure free. That's fantastic, but I think we have to be careful on how we interpret that and what conclusions we draw.

The only other thing about safety, and then I'll move on here, there's about 15.5 percent of patients who had serious AEs or significant AEs, not serious, but SAEs in the operative period and immediate post-operative period, and most of them were replacing leads and infections, and that's a fairly high number in my opinion, although I note this is probably similar to other DBS situations, and so I guess perhaps if one accepts that as part of DBS, it's okay.

I am concerned a little bit about the depression and the memory complaints, even though objectively on neuropsychological testing there isn't. I'm concerned that patients are complaining about this, and certainly if this is approved, that has to be strongly listed as a possible complication.

DR. ENGEL: Can I comment on that?

DR. HURST: Sure.

DR. ENGEL: You know, it's also well known that depression is a consequence of a reduction of seizures. I mean we see that postoperatively in surgery all the time, but it's transient, you know, during the first year, they become depressed, and it goes away, and there are mechanistic explanations for that which are hypotheses at this point.

DR. GOOD: Right, and I acknowledge that. The last thing I would say, this is a technical thing, I'm a little concerned about the battery life. I would hope that that can be improved. This is a minor issue, but gosh, a lot of these people had their battery changed out three times. The guy that committed suicide, although it has nothing to do with the suicide, was going in for his third battery change out, and I would certainly like to see a longer life of the battery, but that's a minor issue.

DR. HURST: Dr. Barker.

DR. BARKER: I would like to say something that I think a number of the other Panelists have already said, which is that I think we're placed in a very difficult position here because in one way, the short-term evidence has this huge sideshow of the p-value that, is it .5? Is at .04? Is at .06? Depending on whether or not one guy had what sounds like a really bad afternoon, and that guy is here to tell us that he thinks we should discount that. I don't think any humane physician would want to see a device that maybe helped 110 people not released to the public because of something like that or because one guy's girlfriend counted seizures different than his mother did.

On the other hand, the best estimate of the effect of turning the device on during that brief period is pretty seriously unconvincing. It boils down to a handful of seizures, measured by a method that I think we have to have serious reservations about. None of the secondary endpoints showed any benefit. There weren't any significantly more patients who had 25 percent less seizures or 30 or 50 or 70, unless you look at one specific month, and in addition, the patients who were most likely to recommend the device were the ones whose device hadn't been turned on. The quality of life measures showed no benefit. The neurocognitive measures, as I understand them, showed no effect. Really endpoint after endpoint with a negative result that sure makes it look like there wasn't any difference between those populations.

And then Dr. Spencer gets up and says, well, what about the 61 percent reduction in seizures in the long term, and I think that the nature of the trial design, although it was well intentioned and patterned closely after successful use for other devices, has left us really in I think what's called a cleft stick, that looking at those short-term results is very unconvincing and yet you could be denying approval to a device that reduces seizures by 60 percent in 100 people, and I think that's a real downfall of this trial design and something that is incumbent on people who care about these outcomes to improve as quickly as possible or else there's going to be a series of potentially ineffective devices that are going to be approved.

DR. HURST: Thank you. Dr. Paolicchi.

DR. PAOLICCHI: Thank you. My comments are similar to those that have been spoken also by the Panel. We have a difficult charge, and our charge is to look at both the safety of the data and evaluate it independently, as well as the effectiveness of the data.

However, from a clinical perspective, and in one-to-one patient situations, we don't analyze those things independently. We analyze those things as a group. So looking at the statistical information, yes, it's been presented very coherently in many different models. Again, it's concerning to have statistical data that we're relying on to make a significant decision determined by whether we add one patient or not. One would prefer a robustness, to use your term, of statistical data to make that decision.

I'm also quite stricken by the secondary efficacy times. There's been many other treatments for epilepsy where the primary may have been misjudged in a trial, but the secondary features are extremely robust and suggest to the people making these decisions, the Panel or the sponsor, that while we really have something here and designed our initial hypothesis incorrectly, that there's efficacy here, but it's primarily from the secondary factors. And the lack of no secondary response is therefore concerning and again puts us at some risk for the robustness of this.

So counterbalancing that, with the safety data, one is concerned about depression in these patients. It's severe. It can cause loss of life. You know, that's pretty significant. One doesn't see other qualities that suggest it would make a huge impact also on life other than seizure reduction, and again we don't have good quality, good parameters to sort of base this on, and it goes back to this is a surgical device. You know, we can stop the drug when it causes a rash. We can stop a drug when it causes your labs to go out of kilter.

This is a surgically implanted device. There is some considerations regarding its implantation. I'm looking at the data that, you know, 14 leads in 9 subjects have to be replaced because of improper treatment, and as mentioned by Dr. Barker, 65 IPG replacements were required as well. That's a lot of surgeries. It's a lot of surgeries in a difficult population that may have other medical constraints as well.

So we have a concern regarding a balance between lack of robustness and clean statistical evidence of an efficacy regarding some true concerns regarding its safety. I think this is a very, very challenging Panel to sit on at this time.

DR. HURST: Thank you. Dr. Chugani.

DR. CHUGANI: I was making a list of all the comments I was going to make, and I think this Panel has touched upon most of them.

I just wanted to point out that epilepsy is not one disorder. It's many different. It’s quite a heterogeneous condition, and I'm sure this population is going to be very heterogeneous, and when you use a treatment for a group like that, you're going to expect some outliers. I think most of us who take care of epilepsy patients, we see outliers. We see people who don't behave the way they should. You know, we're told that if you have a sodium channel mutation limit or lamotrigine, it's going to make you worse, but I have one patient where lamotrigine makes them better, and so you've got that strange outlier. So it's a very difficult disorder to understand, and so the outlier things doesn’t bother me at all and I think those of us seeing patients like that.

But what I really wanted to see was a much better characterization of the population that was studied, and I see that is quite heterogeneous, but then on the other hand, those of us that take care of patients like that also realize that when you have intractable epilepsy, and I take care of kids, and a few adults, but mostly kids, I can tell you that if everything else has failed, the quality of life is very, very poor. So these people, they would welcome any new treatment that has a glimmer of hope. They're not expecting total epilepsy control. If you can cut down their seizure frequency by about 25, 30, 40 percent, they're happy. It changes the quality of their lives. So it's a difficult Panel, I agree.

DR. HURST: Dr. Ravina.

DR. RAVINA: I think I'm in general agreement with what many of the other Panelists have said. I think I'd probably say it in a different way. I think regardless of the analysis plan, with or without the outlier, what we see is that the driver of the efficacy signal is really in that final month of the blinded period. And so we have one month of efficacy, and beyond that, in reality, it's basically very difficult, if not impossible, for us to discriminate efficacy with this control group beyond that period.

So the question becomes is a month of efficacy adequate and the patient population is in their 30s, it's a chronic disorder with surgical therapy, and so I think it's very limiting to only see such a short blinded period.

The other issue that was raised by a couple of the Panelists is that the secondary outcomes don't speak to the clinical significance of that reduction in the rate of seizures. We would expect the rate of seizures to be a necessary condition to improve some of those secondary outcomes, and that would not happen without reduction in seizure frequency, but it would be much more reassuring to see internal consistency in the secondary outcomes.

I think the other thing, it was mentioned about the design, effectively what we're testing or what was tested in this design is stimulation versus non-stimulation, and I think a design that compared best medical management to surgery with stimulation would be informative in other ways. In fact, what we have here in front of us may underestimate both the treatment effects as would be seen in practice but may also underestimate the true side effect profile compared to medical management. It's difficult to know.

I would say finally, overall, I'm impressed by the relatively small overall sample size here compared to the potential clinical use of this device, and because of that, we, in fact, have very wide confidence intervals about some important parameters such as SUDEP. So while the point estimate for SUDEP appears to be approximately consistent with historical data, the confidence interval includes rates that are twice as high. So I think there's a lot of information that is missing about safety.

DR. HURST: Thank you. Ms. Peterson.

MS. PETERSON: Thank you, Dr. Hurst. One of the interesting challenges and opportunities of being the consumer representative is that while you get to dig into the data and think about statistics and study design, you also to get to step back and look at the 35,000 foot level, kind of where the patients live.

Our discussion so far has really looked at the science and the statistics and in particular this question of how the data should most properly be analyzed and what that means for us.

I've sat on a number of Panels over the years, and from the top level perspective, you know, with some devices, when you look at the data in the presentations, you see either death or some other very, very serious adverse events that pretty much tell the story right off the bat in terms of what the Panel wants to do with its recommendations.

I think today with DBS things are not so clearcut. We have some data. We also have an outlier. The statistics concerning the inclusion of that outlier can be very concerning. At the same time, that patient came forward to share his story and to talk about the challenges and the opportunities he's experienced since having the device implanted. And from what we can see, it looks like the patient and his physician working together have found a way to make the implant work for the patient such that his quality of life has improved, which is really what we all want as our end gain.

At the same time, when we look at the secondary endpoints, we see an increase in depression and cognitive problems, but we also see a decrease in injuries.

I'm sure you know from your practices with patients that people have different priorities and tolerances for side effects. Some people may be willing to accept a bit of cognitive change to gain some ability to get out in the world more because of the reduced possibility of injuries, where others may value that mental function and prefer it to the increased risk of injury.

It may well be that DBS is not going to be something that really works for everyone, but that doesn't mean that with further study and understanding of what's happening, that it can't be a useful approach for some patients and perhaps certainly a front-line option for people who have tried other things and not had success or not been able to get the quality of life that they're really seeking.

I'm not going to address the statistical analyses question. I think there are experts here that are more qualified to do that than I am, but I do hope that as the Panel goes forward with its recommendations, that it does not preclude further study, whether that be in other trials or a different type of analysis or supplemental studies of this technology because we really see an absence of death and the extremely severe adverse events that preclude other things, and there is also some evidence that some patients are helped. Thank you.

DR. HURST: Thanks, Ms. Peterson. Mr. Halpin.

MR. HALPIN: Thank you, Dr. Hurst. From an industry perspective, I just wanted to comment on a couple of points.

First, this is an expanded indication for a device which is already on the market for two other indications. I think from a hardware and implant point of view, Medtronic does have extensive experience with this product, although not in this new indication.

The other thing I wanted to mention briefly is the concept of blinded clinical trials with surgical devices. This is a very difficult area to achieve success, in general, because in order to blind the trial, you have to artificially alter the control from what might be an ideal control to one which will allow the patient or a blinded evaluator to not know which treatment has been selected. So I think that presents some challenges. We may have seen some of those today in terms of how you differentiate the implant versus the stimulation effect.

And I think the third point, when you're looking at permanent implant product, we have a short amount of efficacy data in the four-month blinded period, yet if you look at the durability of product over the one, two and three year time point from what they have now, that seems to reinforce that the product does continue to work over a long time period. And that's it.

DR. HURST: Thank you. Dr. Engel.

DR. ENGEL: Yeah, as a scientist, I have a lot of respect for statistics, but as a clinician, I have problems with it and, you know, do you go with a single number or do you look at the totality of the situation, and this seems to hang. I think everybody is agreed that the blinded period is the important period here, and do you accept one number, or do you get rid of the outlier, or do you just look at the last month because you accept the fact that there is a surgical effect that's transient that really disappears by the fourth month?

But I have a stupid question for the statisticians. Is the difference between 0.5 and 0.6 statistically significant?

I mean it's 0.6 if you don't accept the outlier and you look at the whole time instead of the fourth month. Is that a statistically significant difference from 0.5?

DR. EVANS: Are you talking about a p-value? Is that what you're talking about? You're wondering whether 0.5 or 0.6.

DR. ENGEL: Yeah. We're talking about tiny little differences.

DR. EVANS: No, I agree. I agree. As a matter of fact, I am in full agreement that the medical community in general puts far too much reliance on a p-value. Okay. I'll say very much. So you're talking about a p-value.

On the one hand, in this particular case, the point estimate, the effect size, clinically, neither mean or median or whatever estimates actually don't change very much whether you include this patient or not. It's the p-value that sort of wobbles.

All right. I think we do spend too much time or over-reliance on the p-value, and as I mentioned before, there's nothing magical that happens at 0.5. That's very clear.

So let's be clear what the definition of p-value means. I'd like to take a poll to see how many people actually could define it, but I'll tell you what it is, okay. A p-value of .5 means that if there were truly no difference between the two arms, in a world in which the intervention had completely no effect, the probability of seeing the data that you just saw is 50 percent. So what happens is that when you get a small p-value, less than say 5 percent, that means the probability of observing the data you just observed, if you lived in a world in which the intervention had no effect, is very small, which means there's probably something wrong with that assumption. Not necessarily. It could be just a rare event, rare observation. The fact that we use an 0.5 cut point says that when there's no effect to the intervention, we're willing to live with a false positive error rate 5 percent of the time.

Okay. Now, p-value doesn't tell you, it doesn't tell you anything about the magnitude of effect, and as I just mentioned, the estimate of the magnitude of effect in this particular case barely changes, or at least the one I'm remembering, the FDA presentation with and without the outlier, was an estimate of I'm thinking, I don't know, 2.5 seizures per month or maybe it was 3 or 4. I can't remember.

DR. PAOLICCHI: No, you're correct. It's like the 2.3 mean reduction with the adjusted means, negative 2 with an alternate analysis going to negative 2.5 --

DR. EVANS: Right.

DR. PAOLICCHI: -- with a GEE negative 4. So that number is very low.

DR. EVANS: Right, and to answer, do we put all of our eggs in one basket and rely on one number, I say no, very clearly not.

So let's suppose as we just said that the estimate, at least these particular estimates, are fairly similar, whether you include that patient or not. It's the p-value that really jumped.

So let's suppose the truth is that this intervention does decrease relative to the control group, your number of seizures per month by 2.5, 3 seizures or whatever it was per month. Is that clinically relevant? In this population, the population --

DR. ENGEL: Are you asking that?

DR. EVANS: Sure. I think it's a very important question.

DR. ENGEL: Okay. I think personally the seizure number really is not clinically relevant at all. I think what's relevant is the percentage from baseline. When you, as has been discussed over and over again, again as a clinician, when you have a variability of seizures from 6 to 600, and you don't know which patients have had the 2 or 3 decrease, it could be meaningless. It's a percentage decrease. So we're dealing with a whole lot of different things here but, you know, people are looking for something robust. I think just as a reasonable person, it looks to me like it's rather amazing that this study has done what it has in three months given the outlier, and given the fact that there was an effect of the surgery, this is a robust effect, and to haggle over whether it's 5 percent or 6 percent, using the calculations that you want to use, seems to me like we're arguing over peanuts.

DR. EVANS: Can I follow up if I may? So 5 percent or 6 percent, I'm not following what you're saying.

DR. ENGEL: Well, you say that .05 means you have a 5 percent chance of being wrong and .06 means you have a 6 percent chance of being wrong.

DR. EVANS: Right, right. But that's not what we saw here either. So I'm not sure what --

DR. BARKER: I think there's a misunderstanding maybe in that the difference in the analysis with the outlier was .5. In other words, you would make that observation 1 out of 2 times, and without the outlier, it's .05, which is 1 out of 20 times. I think you guys may be talking a little at cross purposes here.

DR. ENGEL: It was .043.

DR. BARKER: That was with person B also excluded. So with the outlier included, the p-value was 0.5, or a 1 out of 2 chance of making a mistake. With Subject A excluded, it's .04 or 1 out of 20, 1 out of 25, and with Subject A and Subject B, it's .06. So it's Patient B who makes the real splitting hairs difference here. The difference I think with the outlier A included or not included simply points out how poor this analysis is at capturing the average person's experience.

DR. RAVINA: Can I --

DR. HURST: Yes, Dr. Ravina.

DR. RAVINA: It's kind of a follow-up question. I do think that the outlier discussion is becoming a bit of a distraction because the estimate of the treatment effect is basically the same. So I don't think it's all that productive to harp on that, but I would like to come on back to the question of the clinical significance of this issue of percent reduction or the absolute number of seizures, the rate per month. I think, you know, we go through this in all kinds of different trials. It's difficult to know, and that's why typically we anchor that primary, the clinical significance in something else, quality of life, responder, global, clinical impression, and that's where I thought we would see something in some of these secondary outcomes and we didn't.

So, you know, aside from all of us basing our own subjective views on what is a significant number of seizures, a clinically important number of seizures, I guess I'd ask some of the epileptologists, are there any anchors in the secondary outcomes or the other planned analyses that point to clinical significance, and again, it's only one month, that 3-4 month, where we see any real reduction, regardless of the analysis plan between the two groups.

DR. HURST: Yes, Dr. Privitera.

DR. PRIVITERA: I wanted to clarify a statement that I made before about some of the secondary outcomes because a lot of people are now talking about the secondary outcomes. When I made my original comment about secondary outcomes, I was really looking just at efficacy secondary outcomes, responder rate, seizure-free rates, and among those, really the only one that would likely be positive would be the responder rate. It's very unusual in any clinical trials of antiepileptic drugs to really see seizure-free rates that really discriminate between placebo and the active drug.

The other secondary outcomes, I think we have to be very careful about interpreting, like quality of life and depression, patient satisfaction. At least in my experience, and I think in the experience of many people that have done the quality of life information and clinical trials, the very important driver of quality of life is depression. So if you have a treatment, for example, an antiepileptic drug, and two antiepileptic drugs are completely equal in efficacy and one has an antidepressant property and the other one does not, you see dramatic improvements in quality of life in the one that has the antidepressant property, and since we're not looking at a treatment that we're evaluating for depression, I think we have to be very careful about looking at quality of life as a secondary, you know, as an outcome that we really think is going to be positive because unlike some, for example, the Vagus Nerve Stimulator, which does seem to have some antidepressant effect, this DBS device, at least in the epilepsy population, doesn't seem to be antidepressant.

So I just wanted to clarify that. When I was saying that I was disappointed that we didn't have secondary outcomes, I was thinking more of the efficacy secondary outcomes and not really sort of quality of life.

Going back to another question that was asked which is the number of seizures changed, I, having done dozens of clinical trials with antiepileptic drugs, don't look at the seizure frequency reduction as a measure of how important a drug would be in my clinical practice. I just look at it as, in this population, was it a factor or was it not? You know, we see many people who can have a 50 percent reduction in seizure frequency. It makes no difference whatsoever. Other people who have a 50 reduction in seizure frequency have a dramatic effect. Obviously anybody who becomes seizure-free under treatment has a dramatic effect.

So even if I have a treatment, a new treatment that I would give to 100 patients in my clinic, if I have 10 people that do really well on that treatment, to me that's a worthwhile treatment introducing. And so I think in some ways, you know, there is a dichotomy between the clinical judgment about whether a treatment is effective and the randomized, prospective, double-blind, clinical trial being statistically significant or not and can argue about what p-value is there.

But I think the more important thing though is just the secondary outcomes. I mean we'd love to have them positive, but I think there are some other drivers of the secondary outcomes that may not really reflect what we're interested in looking at.

DR. HURST: Thank you. Dr. New.

DR. NEW: I was just going to say a couple of things. You mentioned about one month of data. It's unfortunate. It's one out of three basically, and that makes it very hard. And so it may be, you know, we're all used to looking at papers and reading them and looking for scientific statistics, you know, scientifically significant statistical results to publish them, but luckily that's not the charge here.

We're trying to figure out if this was a clinically significant intervention, and as Dr. Chugani mentioned earlier, the patients are desperate, and for them to have anything that impacts them is a big deal, and I think that's manifested in two things, the long-term reduction rate seen in this study and the fact that at two years, 80 percent of the patients said they'd go through it again. Knowing the results of the study -- I mean I think when you look at a clinically significant effect, if you put somebody on a drug that two years later, they said, yeah, I'm glad I'm on this drug, it's had a positive impact on my life, I don't think you'd have any doubt, you know, sitting in your clinic, whether you'd write them a renewal prescription or not. So, you know, that's the one thing about this. I think the statistics are tough. The way the study is designed is difficult. At least we do have a historical cohort within this same patient population, but it's obviously limited statistically as Dr. Evans has told us, but luckily there are a couple of things here that point to pretty strong clinical significance in a desperate population.

DR. HURST: Thank you. Yes, Dr. Jacobson.

DR. JACOBSON: I guess you know you were talking about other aspects of epilepsy, and in both groups, the most severe seizure improved, as did the seizures that were partial to generalized, and it's often the generalized seizures that really are associated with injury.

DR. HURST: Dr. Engel.

DR. ENGEL: Because we didn't talk too much about severity, this chart number 53 shows that it was the non-disabling seizures during the blinded phase that were no different. The complex partial seizures and the most severe seizures were different, close to .05 or .05.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Yeah, I just wanted to make another comment on that patient satisfaction data. Because I certainly agree that we look at statistics from a research perspective, and then we apply it to our clinical practice, but patient satisfaction data is extremely important, and I think there's a real concerning piece of data, which is that you'd have to be honest and say that 92 percent of the patients liked the device if it wasn't turned on or they recommended it if it wasn't turned on. I mean that's actually a piece of data that we have in front of us that obviously we'd have to consider sharing clinically, and it's very disturbing, how to put that into the overall --

DR. BARKER: But there's some benefit of just implanting the device.

DR. PAOLICCHI: Correct.

DR. HURST: Dr. Barker.

DR. BARKER: I have to interject a surgical perspective here, that I have seen behind-the-scenes data on extensive numbers of patients, and it is possible for there to be very high patient satisfaction with an operation that absolutely does not work. So I think that the presence or absence of patient satisfaction with an operative procedure is tricky to interpret.

I wonder if I could ask a question of the people on the Panel who really have massive epileptology experience. When you look at how this cohort of 100 people was assembled, what we would all like to see is a randomized trial that says that at the end of 3 years, there's 61 percent seizure reduction in the patients who were treated and 0 percent in the ones who were not. That would be so compelling that we wouldn't be here today.

How close do you think the observation of 61 percent fewer seizures after three years of this clinical trial experience with the selection, with the patients who had relatively short durations of seizures before going on, with the extra attention that's given to them through the whole trial experience, how surprising would that be compared to natural history if this procedure hadn't been done?

DR. HURST: Dr. Privitera.

DR. PRIVITERA: If you told me that at the end of 3 years you had 61 percent seizure reduction in one group and 0 in another, I mean there's no question that that's not the natural history of this disorder, at least in the patients who I take care of and who I would enter into trials like this, people with 3 and 4 and 5 and 6 seizures, this was at least 6 seizures per month. So the long-term data, you know, both -- I forget the term they used for it, after the blinded phase, was the unblinded phase and then the long-term follow-up data, I think, are strongly suggestive of an effect, but I think we have to be very careful about the biases and things that could be there.

Do I believe that the 61 percent at the end of that long-term follow-up phase is important for many patients and would really make a difference in patients? I think I would have to say yes, and is not unlikely to be natural history in this kind of a population.

DR. ENGEL: I think the issue is whether there are data, and this is a common observation in all the VNS and other stimulation studies, that it gets better over time, and I'm not aware of any equivalent data that's been looked at, but there have been a number of epilepsy surgery studies where patients who have had surgery have been compared with patients who didn't get the surgery, and nobody has ever mentioned that the ones who didn't get the surgery got better over time.

DR. HURST: Dr. Chugani.

DR. CHUGANI: I just wanted to touch upon that and then bring up a different issue. Not only is it with devices that you get better over time, but even with diets, like the ketogenic diet is very well known that there is a time effect, they do get better, and they're cognitively better and everything else.

Now, I wanted to touch upon this effect of placing the electrode and therefore creating a lesion, if you will, in the anterior thalamus and whether that has an effect and then there's a further effect with the stimulation. There are ways to quantify that, and I'm just wondering whether the sponsor has thought about that, assuming that there isn't much of an artifact effect, by doing a MRI, which we have to be convinced it's safe, but you can actually quantify the amount of fibers that have been destroyed by doing a diffusion tensor tractography following the lesion, well, I say the lesion but the placement of the electrode, and that's something that would be very useful to learn in the future, I think.

DR. HURST: We're going to go ahead and move into the FDA evaluation of their questions and delay the break until after that evaluation of the questions.

So if Mr. Marjenin can come up, and he will put the questions up on the screen, and then we'll need to get a sense of the Panel as to the general belief with respect to the answer of each of these questions as well as any concerns that people might have regarding the subject of each of those.

MR. MARJENIN: Okay. So the first FDA question to the Panel today is the definite/probable/possible SUDEP rate for the PMA study cohort was calculated to be 9.2 deaths per 1,000 person-years based on the three deaths that occurred after the completed portion of the baseline phase, and is this SUDEP rate acceptable for the proposed population?

DR. HURST: Dr. Nikhar.

DR. NIKHAR: You know, from the discussions this morning, I think the cohort death rate from the historical data was 9. So I think this is comparable. So yes.

DR. HURST: Dr. Privitera. And we can just go right around and get everyone's opinion.

DR. PRIVITERA: The answer is I don't know. I think this is something that needs to be followed up in a postmarketing study because I think it's such a rare situation that we don't know at this point, and I don't see a signal here that makes me think that SUDEP is very likely to be higher in this group, but I think it needs further study.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think it's compatible with the severity of this patient population.

DR. HURST: Dr. Evans.

DR. EVANS: I don't know either. I would suggest though that they -- I see that their historical data for comparison, I would suggest that they get some estimates of uncertainty associated with these so they can be appropriately compared.

DR. HURST: Dr. New.

DR. NEW: I think the answer is yes, it's compatible but that the concerning part was that confidence interval that somebody else raised, and I do think it needs to be followed up in a long-term post-approval study if done.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: Yes, it's compatible.

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, we know that SUDEP increases with the severity of the epilepsy, and these patients have very severe epilepsy. So given that this is in the same ballpark as the VNS patients that don't have such severe epilepsy, I think it's compatible.

DR. HURST: Dr. Good.

DR. GOOD: A small number of patients, but it probably is compatible.

DR. HURST: Dr. Barker.

DR. BARKER: I agree. It's acceptable but needs further study if the device is applied to more patients.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Concur, compatible but more study.

DR. HURST: Okay. Dr. Chugani.

DR. CHUGANI: I agree. I think it is compatible. It's about the correct ballpark.

DR. HURST: Dr. Ravina.

DR. RAVINA: Agreed. I'd just like to see a tighter confidence interval.

DR. HURST: Ms. Peterson.

MS. PETERSON: Agreed with the provision for further study and monitoring.

DR. HURST: Mr. Halpin.

MR. HALPIN: Defer to the medical folks on the Panel.

DR. HURST: Thank you. My sense from this is that the Panel generally does believe that this rate is acceptable but there is a role for significant follow-up in a postmarketing environment. If anyone disagreed with that, then --

Dr. Eydelman, is that adequate?

DR. EYDELMAN: Yes, thank you.

DR. HURST: Next question, please.

MR. MARJENIN: Thank you, Dr. Hurst.

Question 2, five subjects experienced status epilepticus and five subjects had seizure-related adverse events upon initiation of stimulation, which included Subject A. Do you believe that these seizure-related events raise concerns regarding a reasonable assurance of device safety for the proposed indication?

DR. HURST: Dr. Nikhar.

DR. NIKHAR: Yes, there is a concern about increased seizures following the stimulation including Subject A. So I'd say yes.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I think that it's clear that some of these patients had increased seizures, but I don't see that being a major concern in this population from my perspective.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think it appears that the procedure of the device is associated with increased seizures, and that would be important for patients to understand if they underwent the procedure. It would also mean that they would ideally be treated in epilepsy centers where people would be used to this, where this phenomenon happens all the time.

DR. HURST: Dr. Evans.

DR. EVANS: I'll defer to my clinical colleagues.

DR. HURST: Dr. New.

DR. NEW: Yes, it appears that initially turned on, the device caused seizures in patients, and perhaps it can be addressed by changing the initial stimulation parameters used in the future.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: I don't know, and I would defer to my neurologic colleagues.

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, I agree it's a risk. I don't think given the circumstances it's a tremendous concern, but it's something that needs to be looked at.

DR. HURST: Dr. Good.

DR. GOOD: Again, a very small number of subjects, but it's reassuring that by changing the parameters, that all of these got better. So I would say it's a concern, but you can deal with it.

DR. HURST: Dr. Barker.

DR. BARKER: It doesn't seem like a prohibitive risk to me, and I would imagine the postmarketing studying could be designed to ask a scientific question about how to improve it.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Yes, it seems to be a factor, and it may want to be a consideration by the sponsor and recommendations to physicians on how to handle that risk. I think it will pose some definite patient logistic issues. For those of us who see patients, who come from very long distances, and who are limited by how long we can keep patients in an inpatient area, it may want to set up some safeguards such as not having the patient leave the area locally, being seen the next day with an EEG.

Two things I was struck by, by these adverse events is that

Patient A, sir, didn't seem to recognize his as typical seizures types. So that may be missed, and the second patient who was in non-convulsive status, only presenting with confusion, that wouldn't necessarily have been appreciated.

So there may want to be some definite modifications that the sponsor recommends for potentially a post-op visit the following day with an EEG to make sure that there aren't more subtle clinical events that need that modification or, number two, obviously the patient in non-convulsive status, a need to be controlled.

DR. HURST: Dr. Chugani.

DR. CHUGANI: I fully agree with that. I think that this is of concern, but I think that it's not enough of a concern to abandon this approach. I think that we need to learn a little bit more about this to try to understand how we can prevent that in the future.

DR. HURST: Dr. Ravina.

DR. RAVINA: Agreed. I think it's a manageable risk, but I think it really speaks to the importance of the way this is rolled out and used in the community at whatever point. I could imagine this being a much bigger problem among less sophisticated users, and so it may speak to the need for highly refined training programs and restricted use and monitoring for this particular event.

DR. HURST: Ms. Peterson.

MS. PETERSON: I'll defer to the clinicians on the Panel with regard to the medical aspects of the question. I will say that patient education, provider education, and close management of the environment in which the device is implanted can go a long way towards reducing the risk. The population of patients who would be interested in such a device is likely to be highly motivated to prevent this kind of side effect and to want to work with the physician to get it right so they get the maximum benefit from the device. So I think it's manageable.

DR. HURST: Mr. Halpin.

MR. HALPIN: I would agree with the education and training component.

DR. HURST: Thank you. Dr. Privitera.

DR. PRIVITERA: I just want to make a quick comment that this identification of an at-risk subgroup could potentially be one of the outcomes for a postmarketing study.

DR. HURST: So my sense would be that the Panel does feel that there is an increased risk associated with this. It's certainly not a prohibitively increased risk that can and should be addressed by focusing on the consent labeling, stimulation parameters when the device is initially implanted, as well as education for both the patient and the physicians managing the device.

Dr. Eydelman, is that sufficient?

DR. EYDELMAN: Thank you.

DR. HURST: Thank you.

MR. MARJENIN: Moving onto Question 3, one suicide occurred during the study. There were seven additional subjects with events related to suicidality, including two subjects who made suicide attempts and five subjects with suicidal ideation, and more subjects in the active as compared to the control group reported depression and anxiety, and do you believe that these events raise concerns regarding a reasonable assurance of device safety for the proposed indication?

DR. HURST: Dr. Nikhar.

DR. NIKHAR: So like the previous question, I think there is a concern, not insurmountable, and I think an awareness has to be made to both the treating physicians and the patients about the heightened depression and anxiety risks. So a small concern.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: Similar to the last. I think it's a concern. It's a real finding. I don't think it would obviate an approval for such a treatment. The only question I have, though, was the POMS which was used as the screen which was not different between the two groups, an adequate assessment, and should some other different assessments of depression be added into a postmarketing study that potentially could alert clinicians to the patients who may be more susceptible to worsening of depression or may. For example, we use the NITTI (ph.) which has a question because neurologists in general I think are notorious at not asking questions about depression on regular follow-up visits, and that might be a good thing to add.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think it would be important to include it in the postmarketing plan for physicians who might not be using any sort of depression screen, but I think another concern might be that some patients have insurance to get neurologic care but not psychiatric care, and they might not be able to get adequate screening pre-implantation or, should depression occur, psychiatric care afterwards.

DR. HURST: Dr. Evans.

DR. EVANS: Yeah, I think it was a concern. I do think that the signals for depression and memory impairment were real, but I'm unclear about how to weigh those outcomes relative to the other outcomes.

DR. HURST: Dr. New.

DR. NEW: Yeah, I do find it concerning. I agree, and I think actually some specific changes probably need to be made in the labeling to address it, specifically in the patient therapy manual. If you look at page 49 and page 50, for example, in the patient therapy manual, it lists when to call your doctor, and there's nothing mentioned about depression or suicidal ideation, which I think should probably be added.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: It should definitely be considered in the postmarketing labeling, and I consider it to be a significant finding of this study, and as part of the neurologic review, irregardless of whether they see a psychiatrist or not, or a mental health professional, it should be reviewed by a neurologic clinic, and perhaps another instrument that is a little bit more thorough and sensitive can be applied.

DR. HURST: Thank you. Dr. Engel.

DR. ENGEL: Yeah, I'd like to see postmarketing studies address whether this is comparable or worse than other effective antiepileptic interventions like surgery and also what the risk factors are.

DR. HURST: Thank you. Dr. Good.

DR. GOOD: I agree with what everyone else has said. I would come back to the patient manual, on number 34, depression, memory impairment, they're mixed in with everything else, like tingling sensation, you know. I mean they're all given equal weight. So I mean I think that has to be improved.

DR. HURST: Dr. Barker.

DR. BARKER: This to me is the weakest part of the safety presentation made by the sponsor. We heard that one patient whose stimulator stopped functioning because of battery failure completed suicide, and we heard about 12 patients whose stimulation was discontinued who did not commit suicide. So what's the confidence interval on that? It would be a question for Dr. Evans, I guess, 30 percent suicide rate?

I think we've heard far too little about the safety of what happens when the stimulation stops abruptly after a long period of stimulation, and I think there was a SUDEP event also while stimulation was off, although it wasn't specified that that had ever been on.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Yeah, I concur. This is a serious risk obviously, and one that we have more heightened concerns about, especially with all of the antiepileptic medications that we use and the appropriate black box labeling that is on those medications.

I also agree with Dr. Jacobson who states that it's often very difficult for patients to receive appropriate psychiatric care. I think that postmarketing studies would have to absolutely address this risk, identify factors that may be significant, and some sort of regular screening device may also be something that the sponsor should add in for the protection of the patients using this device.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I would also like to know what the expectations and whether that was discussed, whether each of the individuals who were implanted were allowed to express what their expectations were because with epilepsy, the patients, sometimes they might be expecting a cure, and if they don't get it, you know, you can have serious -- so I think screening before implantation, a thorough understanding, and probably much of the data are there already but I think to see whether you could identify the ones who are the risk.

DR. HURST: Dr. Ravina.

DR. RAVINA: I agree with the previous comments. That appears to be a risk, one that needs further follow-up, clarification as well as explanation in the labeling. I would also suggest that it would be valuable to look at any connection between the mood disorders and the reported cognitive impairments. They may mediate each other, may be the same subjects. It's just not clear at this point.

DR. HURST: Ms. Peterson.

MS. PETERSON: I concur with the suggestion that we strengthen the patient ed materials and the labeling and also the call for additional study about what happens with patients when the DBS stops after a period of occurring.

DR. HURST: Mr. Halpin.

MR. HALPIN: I agree with the suggestion to strengthen the labeling from the sponsor's point of view to address the issue.

DR. HURST: Thank you. So my sense of the Panel's feeling is that this is an increased risk. It's a significant risk, and it's one that may be particularly hard to recognize on the part of the patient, that follow-up assessment or screening for depression would be a very important aspect of the use of this device, that postmarketing surveillance would also be very important to determine the frequency of this and also try to look into any sort of thing we might do to prevent it. Patient education material and discussion of the expected results might also have an impact of the frequency of depression afterwards.

Dr. Eydelman, is that sufficient?

DR. EYDELMAN: Thank you.

MR. MARJENIN: Thank you. Moving onto Question 4, and unfortunately this one spans a couple of slides. The sponsor failed to meet the prespecified primary efficacy endpoint, which was to demonstrate that the reduction in the seizure rate in the active group is greater than in the control group over a three-month period. And the sponsor proposed two additional analyses, one, excluding Subject A and, two, excluding both Subjects A and B, and here we have a table which again lays out the various p-values and median reductions and GEE adjustment means, and so to continue, at the end of the four-week operative phase, in other words, prior to the initiation of stimulation which wasn't included in the previous table, there was a median reduction of 3.3 seizures per month compared to baseline in both groups.

Statistical significance is reached depending upon the analysis that you use, and the difference in the median seizure reduction from baseline between the two groups is either 2.3 or 2.5 seizures per month. The difference in the GEE adjusted means is either 2 seizures or 4 seizures.

And then finally, the secondary endpoints, the responder analysis, seizure-free days, length of seizure-free intervals, and the treatment failures were chosen to further characterize the clinical significance of a change in the total seizure reduction, and all of the secondary endpoints regardless of the subjects excluded had p-values that were greater than 0.05.

And so the question, in light of the above, do the data represent a clinically significant difference in seizure reduction between the two groups?

DR. HURST: Dr. Nikhar.

DR. NIKHAR: So I feel there's a considerable month-to-month variation which colors the picture, and I don't know whether the effects seen in the one month operative phase is lesion effect, placebo effect, or just a natural cause. It's hard to say. So I'm not convinced that the numbers that have been shown show a statistical difference or at least a meaningful difference between the active and the control group.

DR. HURST: Thank you. Dr. Privitera.

DR. PRIVITERA: As they say, this is the crux of the biscuit, but I think after listening to all the statistical considerations, this Subject A and Subject B, I do believe that this treatment represents a clinically significant difference in seizure frequency.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think that if you accept that there's an effect of the lesionectomy and that it is a device that works better over time, that there is a difference between the two groups.

DR. HURST: Dr. Evans.

DR. EVANS: I usually rely on my clinician friends to tell me what's clinically significant, but I guess I was not convinced that there's a clinically significant difference here due to the sort of inconsistency of similar effects with secondary endpoints and other things like that. And I found it a bit troubling that there seemed to be disagreement on the Panel about what the actual endpoint should have been in terms of clinically relevant endpoint and whether we've got the right endpoint and we're looking at the right thing or not.

DR. HURST: Okay. Dr. New.

DR. NEW: As far as the statistical significance, it's close, and it doesn't bother me to throw out the outlier particularly since even scientifically you don't have to disregard his entire experience. We're just disregarding two days of his experience, and as I mentioned before, I think regardless of that result, I think the device did have a clinically significant difference in the two groups.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: The intervention and the difference between the two groups I believe is significant.

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, FDA agreed that that is an outlier, and I don't think there's any difference between whether you exclude A, or A and B. So I think there's a significant difference.

DR. HURST: Dr. Good.

DR. GOOD: Well, I'm still concerned that the effect is not as robust as I'd like to see. I'm concerned that statistically this is marginal. I'm concerned that there may be too much put on the long-term follow-up here, which I think you have to be very careful about. I'm also concerned about coming up with an indication for something that's going to be widely used and possibly could be used by a population other than what it was designed to be used for in this trial.

It would be nice if there was some way, and I hate to say this, to post hoc look at things in a different way statistically. I think that's what Dr. Evans was suggesting perhaps could be done. It certainly would strengthen the study and make me feel a little bit better about final approval perhaps. That's all I have to say.

DR. HURST: Thanks. Dr. Barker.

DR. BARKER: I think the threshold of 25 percent reduction in seizures was chosen for the power calculation because of a stated or unstated sense that that was what clinically significant means. For patients who have an average of 20 seizures a month, I don't think that either 2 or 4 seizures meets that threshold, although I would say that it certainly could in some subpopulation of the patients.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Again, I am concerned with the statistical data as presented in the blinded phase. You know, that was the money phase. That was where we should hopefully have seen the relevant data in order to make some real good decision from a scientific perspective on its efficacy, and in order to do so, obviously we've spent the greater part of the day discussing who to add, who not to add, whether it's better in the first month, whether that's relevant, does that make too much variation. Those are all relevant questions, but it leads concerns into how much manipulation do we need of the primary data in order to see that effect?

I feel that, as mentioned by the sponsor in their presentation, seizure reduction per patient is probably the most relevant, clinically relevant feature; how much your seizures go down affects you that much. I agree that 2 versus 4 in this very intractable population can make very little difference, but it depends on where your baseline is as that very strong p-value indicated in the evaluation for the GEE analysis.

I also feel like the concern is the benefit of the device as suggested by the sponsor as well as the many speakers who came up, as well as we've seen in other devices for epilepsy, is the long-term benefit, but for that, we didn't have a well constructed trial in order to assess that. That really is where the money should have been in terms of really assessing what the long-term effect of the treatment was and what the safety and efficacy was.

So I feel that the data is leaning towards an indication that there's a long-term benefit, but it's hard to justify with just the data from the blinded study.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I agree. I think statistically it could be more robust. I would have liked to have seen more robust data, but I think overall, looking at the totality clinically, I would say it's significant.

DR. HURST: Dr. Ravina.

DR. RAVINA: I do not feel the results are clinically significant. I think we see basically a difference between the two groups in one month, and that's insufficient given the chronicity of the disease as well as the treatment, and the data are not particularly robust either statistically or clinically in terms of the secondary outcomes.

DR. HURST: Ms. Peterson.

MS. PETERSON: To the degree that a non-clinician can really assess clinical significance, I have to say I'm not convinced particularly. In the public testimony, there was discussion and comments about treating patients rather than simply treating seizures and how seizure count doesn't tell the whole story.

Having said that, I think it's possible that this treatment might prove definite clinical significance in certain patient subpopulations, that we may be able to find certain pockets of patients who would find a major difference in further study.

DR. HURST: Mr. Halpin.

MR. HALPIN: In my opinion, you should remove Subject A and look at the data without Subject A. This seems to be almost a distraction in terms of looking at the data. When you look at the remainder of the data, I think if you compare baseline to treatment effect in the active group, it looks like there is a treatment response. And then if you look at month 4, it does look like it's beginning to separate from the control arm, although there's not a lot of data at that point.

DR. HURST: Thank you. So my sense of this is that there's no good sense of this. It's fairly broad, that there's a range of opinion from not clinically significant to clinically significant.

DR. EYDELMAN: I guess we'll take that.

DR. HURST: And I think we were going to stop now to take a 10-minute break. Very good.

Let me make my little break announcement here. Where is it?

(Off the record.)

(On the record.)

DR. HURST: As we go around again, let's take Dr. Nikhar off the hot seat this time, and we'll begin with Dr. Engel and go around.

MR. MARJENIN: All right. Question 5, the primary analysis compared the data averaged over a 3-month baseline period to the data averaged over a 3-month blinded phase. This approach is preferred because it is less susceptible to monthly variations in seizure counts. The sponsor has provided an analysis that compares the active and control group data in the last month of the blinded phase to the average 3-month baseline period.

Given the month-to-month variability, does the comparison of data from the last month of the blinded phase to the 3-month baseline data provide an adequate assurance of safety and effectiveness for a epilepsy indication? And, if not, how long should the blinded phase be in order to provide a reasonable assurance of effectiveness for a deep brain stimulation device?

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, I am partial, because I'm so familiar with the effect of surgery on seizures, to put more stock in the fourth-month data, and if you look at the, I don't have the slide in front of me, but the slide that shows the month-by-month variation, yeah, there is a very clear spike at four months, and I wonder if some statistical analysis could be done to show that that is a significant spike.

DR. HURST: Thank you. Dr. Good.

DR. GOOD: Well, but even when you look at the fourth month, there's a huge degree of variability, if you look at this month-to-month variation, the graph, and I do think it's bothersome. The question is how long would the blinded period have to be? I don't know the answer, and I sympathize with the sponsor that three months seemed like a reasonable time because they're worried about losing their subjects if you keep going too long, and they made that clear. So there's a certain balance. I think that's what they tried to say in their presentation.

Nonetheless, I am concerned about the month-to-month variability. I don't know what to say except that.

DR. HURST: Thank you. Dr. Barker.

DR. BARKER: I think that the comparison of a single month, even with the physicians I find are intelligent enough to explain almost anything that they observe, and although the explanation that the effect takes time to set in makes sense, if you look at the control population, which was different at what I'll call month four, it was exactly the same at month five. So it didn't take any time for the stimulation to work in those patients. So I don't believe that this is something like a delayed start protocol where you see the same. Now, maybe it's the time after the operation that has to set in, but I don't think that this design allows us to distinguish between those possibilities.

I don't see that there would be any problem with the design where some people's device was turned on after one month, two months, three months, four months, six months, eight months. I don't see that there would be any problem accruing patients to such a study. I don't think that that there would be any problem accruing patients to a study where people were told that for 2 months out of the first 12, your device will be turned off. So I think that those concerns, while real, don't weigh very heavily to me. So I think that the blinded phase could be different lengths in different people, and I think that there is room for creativity in designing a future trial.

DR. HURST: Thank you. Dr. Paolicchi.

DR. PAOLICCHI: Thank you. The first part of the question, I would also answer no. There does seem to be some variation looking at the raw data on that particular month, which is sort of ironic, and in addition, as pointed out, the variability is so wide in that graph.

And then number two is a very difficult situation, and as the sponsor pointed out, asking patients to not have a treatment for a given number of time is very challenging. However, I think Dr. Barker's idea is very good. In other words, implant the device, wait potentially more time to have a postoperative effect wear out, and then do the different blinding versus unblinding, and in that kind of a phase, I would say that three months is very reasonable. The way that other epileptic devices answered that question by having a longer blinded period was to do a low/high paradigm, and I don't know the feasibility of that with using this device, but that's certainly another possibility and allows for a longer period of analysis.

DR. HURST: Thank you. Dr. Chugani.

DR. CHUGANI: Yeah, I think three months is a little short. I personally would have preferred about a six-month blinded phase.

DR. HURST: Thank you. Dr. Ravina.

DR. RAVINA: I don't think the comparison of a single month to baseline is adequate. I don't know how long it should be, but clearly it should be long enough to demonstrate some durability of the treatment effect.

I understand that a consideration in the design was the ability to keep medications constant. That makes sense. However, for a device that is to be used on top of and in addition to best medical management, I'm not sure how important that consideration really is. It should show effects above best medical therapy, which might extend the potential to do a longer blinded period.

DR. HURST: Ms. Peterson.

MS. PETERSON: I'll defer to my clinical and statistical colleagues.

DR. HURST: Thank you. Mr. Halpin.

MR. HALPIN: I just wanted to mention that it does appear that the data tends to trend with the control arm getting worse over time and that the blind was actually verified by the sponsor so that they confirm that patients did not actually know what they were getting.

DR. HURST: Thank you. Dr. Nikhar.

DR. NIKHAR: So the state of the third to fourth month is a statistical battleground essentially in a procedure that's irreversible and permanent. I feel uncomfortable that delegating the decision on one favorable month is appropriate.

Again, I don't know if anyone knows what the right period should be, but Chugani had mentioned six months, and I think that's reasonable, although there'd be concerns about how you deal with those patients during that period.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I have no problem with the statistical analysis, like doing one month, as long as it's proposed a priori. I think the question that I had was whether this was, you know, my understanding was that the protocol said they were going to look for a treatment by time effect and that was not statistically significant, but I mean I think if you say we think that this device is going to improve over time, therefore we want to have an a priori and an analysis that looks at the third month of the blinded treatment, while you're still blinded, where you think you're getting some additional effect, I have no problem, you know, saying that if it was proposed a priori that that would be reasonable evidence of efficacy.

DR. HURST: Thank you. Dr. Jacobson.

DR. JACOBSON: So the question is if a longer blinded period would have showed greater efficacy, I don't know how long that blinded period would have had to be, maybe six months or seven months based on what they showed us, but if you had extended the study, then you might have also wanted to keep track of the most severe seizures because if the two groups started to diverge in that three to six months, then you would have indications that would suggest that one group was doing much differently than the other.

DR. HURST: Dr. Evans.

DR. EVANS: I worry about the selective nature of picking a particular month and not using data from other months that were collected. You know, I'm hopeful that there's an effect, I guess, but I think the operative word in the phrase here is, is it reasonable assurance, and I'm not convinced of that, I guess.

I think in terms of if future trials were examined and the duration, you know, what sort of duration, I think the data from this trial could be used essentially as a forecasting tool. You could look at whether observed trends, and using the word trends in quotations, you know, were followed into the future, when would we start to see something that would really give us more confidence that there's a real effect here, and that could be utilized to plan, you know, studies.

DR. HURST: Thank you. Dr. New.

DR. NEW: I think the answer to the first question is no, I'm not comfortable with using one month versus three months to by itself give a reasonable assurance of efficacy, and in answer to question 2, I think probably for a surgical device trial like this, where you expect some effect to the surgery, that the blinded period would need to be six months.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: I don't believe that the three month period is sufficient, and I agree with Dr. Barker that we ought to be a little more creative in establishing some differences here in understanding the differences, and if there is increases in range and susceptibility, then it would become more evident over time.

DR. HURST: Thank you. So my impression of the Panel's feeling is that while the three month may be adequate in the minds of some of us, that there was definitely a feeling that a longer period, perhaps as long as six months, or even a variable start time, might be a reasonable way to look at this in the future.

DR. EYDELMAN: Thank you.

MR. MARJENIN: Question 6, the PMA contains data on all available subjects for two years or more post-implant. The sponsor believes that effectiveness is supported by the open label phases. However, FDA believes that open label data are difficult to interpret. Given that the unblinded and long-term phases were open label, that subjects could change their antiepileptic medication, that subjects could change their stimulation settings, and that there were missing data, please provide your interpretation of the open label data.

DR. HURST: Why don't we go the same way again. Dr. Engel.

DR. ENGEL: Yeah, I think it's interesting that all these stimulation studies have shown improvement over time, but we don't have natural history to compare it to. We don't know what happens to these patients, and as I said before, the only thing we have to go on is that there have been surgical trials that have looked at patients who didn't get the surgery, and nobody mentioned that they got better. That data may be available to go back and look at; I don't know.

DR. HURST: Thank you. Dr. Good.

DR. GOOD: I said this before. Although I'm gratified to see that there was such positive results, from the open label trials, so many people appeared to have a good prolonged beneficial effect, I'm concerned about making decisions based on open label trials.

DR. HURST: Thank you. Dr. Barker.

DR. BARKER: As I said before, I think the open label data is the biggest effect of any of the data we've seen today, and the drawbacks of not having published natural history data in a comparable population or having some agreed upon prognostic scheme for people who present with a certain number of seizures of a certain duration at a certain age, like we have in cancer trials for instance, that would allow you to stratify by severity and natural history expectation, I think that makes our decision very difficult.

DR. HURST: Thank you. Dr. Paolicchi.

DR. PAOLICCHI: I agree that the effectiveness of the device, as I've mentioned before, may very well prove itself to be more evident in more longer term studies, but I'm going to steal Dr. Privitera's phrase, the a priori assumption, because if that had been their a priori assumption, that a well-designed open label trial would instead show effectiveness of the data, that would have been more convincing evidence rather than using it as the justification when the blinded portion raised such controversy.

DR. HURST: Thank you. Dr. Chugani.

DR. CHUGANI: At the risk of being recruited by the FDA, I must say I agree with the FDA that it's very difficult to interpret the open label data.

DR. HURST: Thank you. Dr. Ravina.

DR. RAVINA: Yeah, I agree. I think the unblinded and long-term data are difficult to interpret. Had subjects all come up to their baseline, we might feel differently about it, back up to their baseline. So I do think it's encouraging, but in terms of level of evidence, it's basically the level of evidence of a case series, and you can draw limited inference from it.

DR. HURST: Ms. Peterson.

MS. PETERSON: I concur with the FDA's assertion that the data are difficult to interpret, and with the physician colleagues who have spoken previously.

DR. HURST: Mr. Halpin.

MR. HALPIN: When I look at the data, it seems to support what was happening at the end of the blinded phase continues to happen out from four months all the way out to three years.

DR. HURST: Thank you. Dr. Nikhar.

DR. NIKHAR: In the open label section, there are considerable variables, and these are likely to color the picture. I would therefore advocate caution. It may be that time will reveal consistent and robust data, but I'm not confident that that's visible in today's discussion.

I'm actually not that bothered about the presentation of the long-term data, which was not mentioned a priori as Dr. Privitera has mentioned, and these things will happen in trials, but again with regard to the specific question, I think there are too many variables to say yes to this.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: The long-term data are supportive, but I don't think they stand on their own as evidence of efficacy.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I would agree with my colleagues. It is striking that in long-term they did so well because we know that people who failed so many medications have a low probability of having such a robust response to anything. So that is certainly a striking aspect of the data.

DR. HURST: Dr. Evans.

DR. EVANS: I think its usefulness all depends on whether you have historical or other data to compare it to. I think it's both useful and difficult to interpret. It's data that gives us more information, but again we don't know what would have happened to similar patients had they chosen an alternative strategy, and we have no way to measure it up against anything.

I would also mention that for the primary analysis in the blinded phase, the quality of the trial was very high in the sense that you didn't lose many patients, and your primary analysis I think only excluded the one or two patients, and that's very good.

Once you get to long-term data, you start to lose more folks, and that means, you know, you run into the possibility that, you know, people who are doing very well, a very select group are staying around, and people who are not doing well, they're going away. And if you only analyze the people who are doing well, then you've got a distorted view of what's going on. So I think I would sort of reassess what we're seeing in terms of either dropout or people who are not completing enough days or whatever qualifications would be very important.

DR. HURST: Thank you. Dr. New.

DR. NEW: I agree that open label data is difficult to interpret. Several caveats were brought up here, and I think as far as that the subjects could change their antiepileptic medications and that they could change their stimulation settings, that doesn't really bother me because that's how the device is going to be used in real life.

The fact that there was missing data, as Dr. Evans has brought up, is a little concerning because you worry about that positive bias effect, that patients doing poorly drop out of the trial, but I think the sponsor showed us an analysis of that with the worse case assumption that still looks pretty impressive in this difficult to treat population.

So the main thing you come down to is the lack of a control group.

Ideally, I guess you'd have a one to two year randomized control trial with best medical therapy versus the surgical device. I'm not sure that's an ethical trial to do. So I'm not sure you're going to get that kind of data.

So the best thing that we have is this pretty short, and I think most of us agree is a little too short, blinded period followed by this long poorly controlled data, and I say poorly controlled, not ideally controlled is probably the better way of saying it. It's not poorly controlled. We have good three-month baseline data on these exact same patients, and there was statistically significant positive results in, what, 99 patients the first year and 81 patients the second year. And I would go back to say that, you know, although I understand the limitations of the poorly controlled are not an ideally controlled group, that that is a clinically significant improvement in a population that is pretty difficult to treat.

DR. HURST: Thanks. Dr. Petrucci.

DR. PETRUCCI: The open label data is difficult to interpret, and without controlling more of the variables in the long-term phase, I think it's equally difficult to continue to try to interpret this. Better control would help us.

DR. HURST: Thank you. I think the general sense would be, and again correct me if people have a different impression, that the FDA is certainly correct in their statement that these data from open label trials are very difficult to interpret, perhaps better interpreted if they're a priori, and they may well reflect the real life utilization of these devices, but nevertheless difficult to interpret.

UNIDENTIFIED SPEAKER: But historical controls are available, and it's appropriate to make that comparison.

DR. HURST: And I think that's reasonable, too, that when and if historical data are available, that that certainly should be used.

UNIDENTIFIED SPEAKER: And it would be more important in the presence of a positive primary outcome. I mean these are strongly supportive data, but I don't think that they stand on their own.

DR. HURST: That's okay, Dr. Eydelman?

DR. EYDELMAN: Accepted.

MR. MARJENIN: Question 7, all subjects received bilateral stimulation to the anterior nucleus of the thalamus, and the proposed indication does not restrict the location of seizure onset. However, the majority of the subjects' seizures originated in the temporal and frontal lobes. Do you believe that there are sufficient data to support an indication that encompasses partial seizure onset from any location as well as multifocal onset? Alternatively, do you believe that the indication should be restricted based on the seizure onset location, and if so, please state the seizure onset location to which the indication should be limited?

DR. HURST: Thank you. Dr. Engel, would you like to begin with that?

DR. ENGEL: Yeah, I don't think we have any idea what population of patients will or will not benefit from this, and personally I don't think we should restrict the use of it, but there should be a strong postmarketing effort to identify subgroups that might respond better.

DR. HURST: Dr. Good.

DR. GOOD: I just don't think there's enough information. You know, there's such a small number that weren't temporal or frontal. I don't think you can draw any judgment or any conclusions.

DR. HURST: Thank you. Dr. Barker.

DR. BARKER: I agree. I don't think the information presented supports any restriction, and the risk profile of the device doesn't seem to mandate that that restriction be generated before it be further developed.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: I think the subjects in the trial accurately reflect the natural history of refractory epilepsy in this population. So I have no objection to that.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I agree with what has been said. I think frontal, parietal, temporal versus occipital, my gut feeling is that it may not be as effective in occipital lobe epilepsy, but that's only a gut feeling, and I see no reason to restrict it.

DR. HURST: Dr. Ravina.

DR. RAVINA: I don't think there's adequate information to draw any conclusions about localization.

DR. HURST: Ms. Peterson.

MS. PETERSON: I defer to the clinicians on the Panel.

DR. HURST: Mr. Halpin.

MR. HALPIN: I defer as well.

DR. HURST: Dr. Nikhar.

DR. NIKHAR: I don't feel a distinction between the two groups is clear at this time. I think some subanalysis is inevitable over time, and I don't think this was the objective of the PMA, and therefore the indication should not be based on seizure localization at this stage.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I think in any trial like this, the actual localization of the patient's seizures and exactly where they spread to, for example, patients who have frontal lobe epilepsy that spread to temporal lobe, is unknown. So I think any restrictions are unnecessary.

DR. HURST: Thank you. Dr. Jacobson.

DR. JACOBSON: I agree with what Dr. Privitera said.

DR. HURST: Dr. Evans.

DR. EVANS: I don't think we have sufficient data to know whether the treatment effect's going to vary much by location.

DR. HURST: Dr. New.

DR. NEW: I agree, insufficient data.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: Same, insufficient data.

DR. HURST: Thank you. My sense is that the Panel believes that there is insufficient information to make any statement regarding a restricted population or a subset that we might preselect would benefit and that postmarketing studies would be very important in order to make a determination as to whether there are any particular groups that might do better or worse.

DR. EYDELMAN: Accepted.

MR. MARJENIN: Thank you. Question 8, the sponsor has provided MRI guidelines which are based on bench and phantom testing that apply to their DBS system, and in addition, the sponsor's proposed labeling recommends that a postoperative MRI be performed in order to confirm proper lead placement. The sponsor has not provided test data on the MRI compatibility of the DBS system with abandoned VNS leads. Fourteen lead revisions were required in nine subjects because the leads were not within the anterior nucleus of the thalamus. Do you believe that MRI compatibility testing should be conducted prior to approval to allow a postoperative MRI to confirm lead placement and to allow MRI use for future medical needs? Alternatively, do you believe that the accurate placement of the lead and patient safety can be assured without the option of postoperative MRIs?

DR. HURST: Dr. Engel.

DR. ENGEL: I don't think we have any data to say that it's okay to proceed with this without MRI evidence, that the electrodes are in the anterior nucleus of the thalamus even though DBS studies for other causes, other diseases have gone ahead in that situation, but I don't think that should happen here.

DR. HURST: Dr. Good.

DR. GOOD: I agree completely. When you think about the SAEs, one of the most important ones was improper placement. So I think you need a MRI.

DR. HURST: Dr. Barker.

DR. BARKER: I'm surprised by the question frankly. Neither FDA nor the sponsor told us how many MRIs have been done in this situation and whether there were any ill effects. I don't know how you expect us to comment on the safety.

I would say that the one thing that I heard that may be relevant is that there is often asymmetry in the anterior nucleus position based on a patient's prior surgery, and my expectation would be that the best possible study would be necessary to get the best results in those patients.

DR. HURST: Thank you. Dr. Paolicchi.

DR. PAOLICCHI: I would absolutely encourage the sponsor to continue postmarketing analysis of the safety of patients with remaining VNS leads and MRI because it will be the case that a large percentage, and I believe it was 40 percent of the patients, actually fit into that mode, and in clinical practice, that may even be a higher percentage in addition from a clinical, practical position that leads to a lot of difficulties in medical centers regarding the safety of these MRIs, and for the sponsor to have that data would be invaluable.

And the second part of the question, I think the data shows a very good reason that there's absolute necessity for both pre and post-MRIs to assure lead placement.

DR. HURST: Dr. Chugani.

DR. CHUGANI: I think absolutely you do need the MRI data. I'm just wondering how much of this safety information we can get from the Parkinson patients because certainly those patients have had MRI scans.

DR. HURST: Dr. Ravina.

DR. RAVINA: Well, we haven't all discussed, and I don't know how much is known about the relationship between the accurate placement and clinical results. So for that reason, I think a postoperative MRI is necessary to determine that. At some point, it may not be necessary, but it could affect both the efficacy, side effects, you know, battery duration and so forth.

I'm not familiar enough with the VNS MR compatibility issues to really know if there's a question about MR with VNS combined with the DBS system.

DR. HURST: Thank you. Ms. Peterson.

MS. PETERSON: I defer to the clinicians on the Panel.

DR. HURST: Mr. Halpin.

MR. HALPIN: Defer as well.

DR. HURST: Dr. Nikhar.

DR. NIKHAR: Yeah, I too believe that MRI is required postoperatively or at least should be encouraged postoperatively, especially with the number of falsely placed leads.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I believe there were approximately half the patients in the study had VNS leads still on. We didn't hear any data suggesting that there's any increased risk if you have VNS plus DBS in getting a MRI. I don't think we have any data to suggest that we should be put additional restrictions on getting MRIs.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think that a post-implant MRI would be essential, but it might be possible to find out from the vendor of VNS what their experience has been with leads because the device has been removed in other patients.

DR. HURST: Dr. Evans.

DR. EVANS: I'll defer.

DR. HURST: Dr. New.

DR. NEW: I think a MRI after surgery to confirm proper location of leads is critical, and there is literature to suggest that it's safe to perform a MRI in VNS patients with the leads only remaining, plus in the trial itself, all these patients got a separate MRI without any evidence of complications. So I think that's sufficient.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: I'm surprised that there are no imaging studies reported for us in the different groups, and I would think it's important to have imaging pre and post.

DR. HURST: So my sense is that the Panel feels pretty universally that MRI post-procedure is absolutely necessary. Postmarketing surveillance would be important to identify any problematic areas with post-procedure MR, that some data from Parkinson patients might be useful in order to predict potential problems but that the manufacturers may have much of that data already.

Dr. Eydelman, is that adequate?

DR. EYDELMAN: Actually the question here was about DBS and VNS, and so the Parkinson's experience is not necessarily pertinent. But I think we heard enough from the Panel to move on.

DR. HURST: Okay. Very good.

DR. EYDELMAN: Thank you.

MR. MARJENIN: Thank you. Question 9, the proposed labeling includes the following: One is a warning, and it's about depression monitoring. During treatment, patients should be monitored closely for new or changing symptoms of depression, and the second is a precaution about patient monitoring. Seizure frequency may increase when stimulation is initiated and adjustment of stimulation parameters may alleviate this effect. Instruct patients to carefully monitor their seizure frequency during the first few days and weeks after stimulation is initiated. And so our questions to you, do you believe that these proposed labeling statements adequately address the potential for depression and seizure-related adverse events, and if not, what modifications would you recommend? And, secondly, do you have any additional labeling recommendations?

DR. HURST: Dr. Nikhar, can we start with you on this one? Sorry.

DR. NIKHAR: With the depression, you know, it's clear that there's a higher incidence at least by the data of increased depression in the active group. I would suggest that the label qualify that there is actually an increased risk of depression. It just mentions that they should be monitored, but I would qualify that there's an increased risk of depression, including suicide.

I would also recommend a time format for this review, whether it's by clinician or via phone call, say within two weeks or one month.

With regards to seizures, I recommend a follow-up with the clinician rather than leave it to the patient to monitor the seizure because there was a change in the seizure type, and there's also a higher incidence of confusion. So leaving it to the patient, I think, poses risks for adverse outcomes.

DR. HURST: Thank you. Dr. Privitera.

DR. PRIVITERA: I think for the depression, it would be useful to add that patients should have baseline monitoring of depression symptoms and then continued monitoring of depression symptoms while undergoing the treatment.

For the seizures, I would consider adding that because we saw seizure frequency changes, but we also saw a change in seizure character, so I might consider changing the wording to say seizure frequency may increase and seizure characteristics may change when stimulation is initiated and leave it the same way.

DR. HURST: Thank you. Dr. Jacobson.

DR. JACOBSON: In the patient and physician training tools and information, you might actually require somebody to document that we've screened the patient for depression before you implant the device, whether that's taking the standard medical history and/or using some kind of standardized questionnaires that somebody could fill out.

Regarding the increase in seizures, you might also use some other tools that are given to the patient with their discharge instructions, not only the idea that the physician or the physician's office calls the patient, hi, how are you doing, but spells out exactly when to call. If you have a history of 6 seizures a day, do you call when you get to 9, or do you call when you get to 12?

DR. HURST: Dr. Evans.

DR. EVANS: I would just suggest that they add warnings on memory impairment and anxiety as well.

DR. HURST: Okay. Dr. New.

DR. NEW: Yeah, I think the depression monitoring warning needs to be stronger and the patient manual, as I mentioned before, also needs to list concern for depression and suicidal ideation as a reason to call your physician.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: We know that this group is very susceptible to depression, and they're high risk, and they ought to be closely monitored pre and screened either by the clinician and/or a tool or both, and there ought to be a labeling precaution put on the device, and I'll leave the area of monitoring for seizure frequency to my neurologic colleagues.

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, I agree with everything that's been said and have nothing more to add.

DR. HURST: Thank you. Dr. Good.

DR. GOOD: Yeah, I agree, too. Again, the patient therapy manual, page 35, 36, there's something that says depression monitoring, but your doctor should monitor it. It doesn't say anything about patients reporting anything, and I don't see anything, unless I'm missing it, about patients reporting a change in their seizure type or frequency. So that has to be strengthened.

DR. HURST: Thank you. Dr. Barker.

DR. BARKER: I think that I agree with everything that's been said but would add that for depression it should say during treatment, and after treatment stops, the patients should be monitored closely and that you've done nothing to prove the safety of the device in patients with a history of suicide attempts or suicidal ideation and that the labeling should reflect that.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: I agree with all the comments being made. I would advocate stronger guidelines for the monitoring of the depression be better spelled out. I would advocate for the clear spelling out of the possibility of suicide, in addition, as Dr. Barker suggested, making it clear that sensation of the device may not be felt by the patient but could be experienced by feelings of suicidal ideation and/or intent.

As to the second part of the question, again I bring up the point that the stimulus-induced seizures may be very different than the patient's baseline. They may not be aware. So a post-op day one EEG may identify change in the status, especially non-convulsive status.

As to the third part of the question, I concur with mentioning anxiety and memory impairment as labeling recommendations for advising patients.

DR. NEW: Can I ask just to clarify? Do you mean post-op or after they're turned on?

DR. PAOLICCHI: Thanks. That's a good point. Right. Thanks.

DR. HURST: Thank you. Dr. Chugani.

DR. CHUGANI: Yeah, I just wanted to reiterate what Julian said about the non-convulsive seizures. I think that's the real risk because if you don't do that EEG, you won't know that your patient is in non-convulsive status.

DR. HURST: Thank you. Dr. Ravina.

DR. RAVINA: Yeah, I agree with the prior recommendations. Nothing to add.

DR. HURST: Thank you. Ms. Peterson.

MS. PETERSON: I concur with the recommendations previously discussed by the clinicians on the Panel.

With regard to additional labeling recommendations, I would suggest something that indicates to clinicians that the success of the device involves a patient/provider partnership and that they may need to invest additional time beyond other types of treatments to make the device successful for the patient.

DR. HURST: Thank you. Mr. Halpin.

MR. HALPIN: I have nothing to add.

DR. HURST: Thank you. So my sense is that there is a pretty universal feeling that the warning should be stronger with respect to both depression and seizures. With respect to depression, emphasizing the possibility of suicidal either ideation or intent, even in a setting where the device might fail or where it appears to be working normally and any change may not be detected by the patient. Baseline monitoring for depression might also be a reasonable precaution, and post-therapy risk and follow-up would also be emphasized.

With respect to the seizures, that should be up to the doctor to follow that relatively closely with the emphasis that both the frequency of the seizures as well as the character of the seizures, to include, for example, non-convulsive status, might appear where that was not present before and that changes to the physician training manual should emphasize that and also in some of the patient training material.

There also might be mention in the label of anxiety and memory loss, both immediately following the operation and during therapy, should also be something to be brought up. Dr. Eydelman?

DR. EYDELMAN: Thank you.

MR. MARJENIN: Thank you. So Question 10, do you believe that the clinical data in the PMA provide a reasonable assurance that the proposed device is safe and effective for the proposed indication and that the benefits of the device outweigh the risks?

DR. HURST: Why don't we begin with Dr. Engel?

DR. ENGEL: Yes.

DR. HURST: Dr. Good.

DR. GOOD: No, not without more information.

DR. HURST: Dr. Barker.

DR. BARKER: I think it's as safe as any brain surgery is. Neurosurgeons have different standards for that than normal people, and I think the balance is stronger that it is effective than that it is not.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: No, not with the current data available.

DR. HURST: Dr. Chugani.

DR. CHUGANI: The answer to Question 10 for me is yes.

DR. HURST: Dr. Ravina.

DR. RAVINA: No, I don't believe the clinical data support efficacy that is adequately balanced with the risk.

DR. HURST: Ms. Peterson.

MS. PETERSON: I concur with Dr. Ravina.

DR. HURST: Mr. Halpin.

MR. HALPIN: I think if we remove Subject A, that I would say that, yes, it does have a reasonable assurance.

DR. HURST: Dr. Nikhar.

DR. NIKHAR: The side effects are not insubstantial. At the end of the blinded phase, 40 serious adverse events and 109 at the end of two years for serious adverse events. I don't know how this compares with the other established DBS and stimulation devices, but there are substantial adverse events, some requiring repeat surgery. So safety side is no. Effective, there's a positive trend seen, but data I don't believe is strong enough, meaningful enough at this time. There's sufficient controversies about the month 3 and 4, and the variability involved with the open label part. So efficacy also, I don't think, is positive.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I believe with the elimination of the outlier, that the efficacy has been demonstrated, and I think it's safe.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: Yes, for safety and efficacy.

DR. HURST: Dr. Evans.

DR. EVANS: For me again the key phrase is reasonable assurance, and I would have to say no. I don't believe that we should get hung up on the one patient or p-value assessment either. I think more of the things that convince me was, listening in the conversations, seemed to be lack of convincing evidence of clinically relevant effect and lack of sort of supporting evidence from secondary endpoints, and that perhaps the strongest signal that I was able to discern from the reports were actually the signals for depression and memory loss and anxiety. So I would say no.

DR. HURST: Thank you. Dr. New.

DR. NEW: I would say yes.

DR. HURST: Dr. Petrucci.

DR. PETRUCCI: The benefits do outweigh the risks, yes.

DR. HURST: Thank you. I think just by a head count, the benefits do outweigh the risks, so far, this unofficial head count. Is that sufficient?

DR. EYDELMAN: Yes.

MR. MARJENIN: And finally for Question 11, and this is the post-approval study. Should I read this entire thing?

DR. EYDELMAN: Yes.

MR. MARJENIN: Okay. FDA's inclusion of a question on a post-approval study should not be interpreted to mean that FDA has made a decision on the approvability of this PMA device. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval, and a recommendation from the Panel on whether to approve a device or not must be based on the premarket data. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered.

The following is FDA's question regarding potential post-approval studies should the Panel find the device approvable following its discussions and deliberations of the premarket data.

Should the system be approved, the applicant has proposed a 5-year continuation of the current pivotal study as a post-approval study, as well as a second group of 50 prospective, non-randomized subjects at multiple centers.

So there are several parts to this question. Should I go through these individually?

DR. EYDELMAN: Yes.

MR. MARJENIN: Okay. So I guess we'll go through these one at a time then.

So, Part A, the sponsor has not proposed a comparison group (for example, best medical therapy) and instead intends to use a patient's baseline seizure rate as a rate of sustained effectiveness. Please discuss if there is need for an active comparison group, and if so, please make a recommendation on the most appropriate comparator.

DR. HURST: Could I just interrupt you?

MR. MARJENIN: Yes.

DR. HURST: This is a long and somewhat difficult question with a lot of statistical implications, and I want to be fair, and I'd like to begin with Dr. Evans on this when you get finished, and then we'll go around beginning with Dr. Evans just to let him know that we're going to start with him.

MR. MARJENIN: Should we answer these one at a time?

DR. HURST: Do you want to do it one at a time?

DR. EVANS: Yes.

DR. EYDELMAN: It's the Panel Chair's discretion, as long as we get the answers to everything.

DR. HURST: I think that's a little bit more reasonable, to do it one at a time.

MR. MARJENIN: Sure. So to address the first point then, please discuss if there is need for an active comparison group, and if so, please make a recommendation on the most appropriate comparator.

DR. HURST: Dr. Evans.

DR. EVANS: So I think that based on discussions we've had here today, that one of the limitations of the study we've been reviewing is that we aren't really able to estimate an effect of implant plus stimulation. We were able to estimate an effect of stimulation but not implant plus stimulation, at least not in an isolated way, and for that reason, I would propose or suggest that they consider some sort of control and may not, given the limitations Dr. Halpin pointed out, that you may not be able to do blinded studies and so on, but having some sort of control, I think, would be very important to put results into context. Otherwise, they're very difficult to interpret, as the discussion we had about open label interpretation today. So I guess I would start there.

DR. HURST: Thanks. Dr. New.

DR. NEW: I think if the device is approved, in a post-approval study, to have a best medical therapy control group which would be the ideal control group would probably be unethical, and I think that the best you're going to be able to is to take a good baseline, the patients themselves, for a few months before they get implanted, similar to the study that we've got.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: I like the idea of having another group to compare it to. That would be an optimal medical treatment group. I'm not exactly sure how we would do that, but I think it's important in a longer-term study to have this comparison group in addition to the group that we have now and we've been studying. So yes.

DR. HURST: Dr. Engel.

DR. ENGEL: Yeah, that's a complicated question because it depends on the question you want to answer, and I think there are a number of questions that could be answered by a comparator group. If you want to know whether long-term patients run down, you might be able to use a historical control group, or you could use best medical care without implanting them with equivalent number of seizures over a long period of time.

If the question is to control for the effect of the implantation, which seems to be important, then there are other study designs that might be implemented, like implanting patients and then waiting for many months before turning anybody on, and then randomizing them based on the effect of the implant, maybe or other things, taking into account the effect of the implants.

I think there are lots of study designs that can be done to answer specific questions.

DR. HURST: Thank you. Dr. Good.

DR. GOOD: Well, it would be nice to get a concurrent comparison group, but I don't know if that's going to really be possible. I think it's going to be hard to do. Best medical management is great, but I think you'd have a hard time. You could pick people who refuse the implant, but that's not a true comparison group. So I think it would be hard to do. I'd like it, but it's hard.

DR. HURST: Dr. Barker.

DR. BARKER: I think this is very clear, the comparison against baseline will be no better and, in fact, likely to be much worse than the information we're seeing today. There should be a randomization against best surgical treatment, which would be resective surgery if eligible or otherwise vagal nerve stimulator implant.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: I concur with the overwhelming ground swell, which this is difficult in that, yes, we would like best medical therapy to be included. How that's done is logistically difficult, and for many of us who participate in trials, that is always a challenge, and whether some creative study design could answer a similar question in the group pretreatment may be another way to address that issue.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I agree. I think we do need a comparison group, and I think we could probably spend many hours talking about the optimal group, but I think that vagal nerve stimulation is approved, that that would be a reasonable group to compare against.

DR. HURST: Dr. Ravina.

DR. RAVINA: Yeah, I do think that a comparator group is necessary for all the reasons that have been laid out. If the device is approved based on the data that we've seen today, I think it will be most useful to have a comparator group that is the same as in the trial before us. That will allow at least combining those groups. You'll have subjects treated in similar ways, and we prefer that the control not have their stimulation on for longer, but I think ultimately pooling the data will be more informative than having a totally different kind of study design.

DR. HURST: Ms. Peterson.

MS. PETERSON: I agree that the data would be improved if we had a comparison group, and I would suggest best medical therapy or, as Dr. Barker had suggested, VNS or surgical treatment.

DR. HURST: Mr. Halpin.

MR. HALPIN: I think that a comparator group helps you from a scientific and local point of view. I think, depending on the question, that that needs to be answered by the trial. You want to be careful about not forcing a particular type of comparator. So I would think some flexibility with regard to how that process is done in order to allow the best answer for the question would be useful.

DR. HURST: Thank you. Dr. Nikhar.

DR. NIKHAR: I do think some flexibility is needed. I think comparison with baseline seizure frequency would help or possibly delaying the blinded phase after insertion of the leads might help clarify the 3.3 seizure reduction that was observed.

DR. HURST: Thank you. Dr. Privitera.

DR. PRIVITERA: I don't in my mind have a design that would measure sustained effectiveness without violating equipoise. So I don't think such a trial, at least I can't come up with an idea on how to do a trial such as this. So I'm not sure that a comparison group would give us any more information than just using the patient's baseline seizure frequency as long as they're in a long-term, open label trial.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think the question of a comparison group with best medical therapy is an interesting idea. I know that many of us have patients who will decline epilepsy surgery, vagal nerve stimulator, and they will decline this because the patient's perception of all of these are experimental therapies, even epilepsy surgery. And so there are patients that might participate in best medical therapy. We all have patients in our practice who are very compliant, but they don't go to that next level. The question is, are they a true comparator group or not? So I don't think it would be impossible to find that group. They might have different sociologic aspects about them compared to the treatment group.

DR. HURST: Thank you. And I think that our sense of the Panel is that a control or comparator group would be very important but also potentially very difficult. Historical control, while certainly not optimal, may be perhaps the best available. Other more creative solutions might include comparison with other best surgical therapy, like resection or vagal nerve stimulator; longer waiting to turn the unit on after implantation might be another possibility.

DR. EYDELMAN: Thank you.

MR. MARJENIN: Thank you. To follow up then on the first part of the question, among the adverse events seen in the premarket study, there were a number related to depression, suicidality, cognitive changes, and seizure activity. Please discuss if an active comparison group would be needed to assess safety as well as effectiveness.

DR. HURST: Dr. Evans, your thoughts on that.

DR. EVANS: Again, I think it depends on whether there might be historical data available in order to put the results into context. If you do, then maybe you don't need it but, of course, you're again limited by, you know, biases of historical data and improving standard of care and, you know, medical intervention over time.

So I think the answer, you know, if you're going to do a single arm trial, you have to envision a way in which you're going to interpret estimates of depression rates and other types of rates, and we need something to compare it to. So the question is what's out there for historical data?

DR. HURST: Dr. New.

DR. NEW: And I think, yeah, this is a tough one. We've sort of already answered the active comparison group question, and we've all said, yeah, it would be good, but it's going to be difficult to actually achieve. And so I think this comes down to in the post-approval study, if the device is approved, that you just have to, as was mentioned when we talked about the depression stuff, specify how that's going to be monitored and probably do so with better scales and with some certain defined frequency of administering those scales.

And regarding the seizure activity, I would think that as we talked about the post, after turning the device on, getting the EEG would be important and also potentially starting at a lower level of stimulation and gradually working up may also be beneficial.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: Again I think the group needs to be formulated, another group, perhaps optimal medical treatment. Perhaps we can look at those that have had previous stimulator implants, like those that have Parkinson's, et cetera.

DR. HURST: Thank you. Dr. Engel.

DR. ENGEL: Yeah, whatever type of comparison group you choose, you have to match them for history of depression.

DR. HURST: Dr. Good.

DR. GOOD: I agree with what's been said. A comparison group is ideal, if not historical information.

DR. HURST: Dr. Barker.

DR. BARKER: I don't think there can be any meaningful comparison for these events with a comparison group because suicide is too rare an event to be measurable in a meaningful fashion, even in a randomized study, and because the measurement of depression and cognitive changes that we've heard about today are not quantitative. They're simply that the patients said they had them. So I don't see how you could compare that meaningfully to any other group.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: I don't think I have much more to add other than, as we have said, that the best medical therapy would be optimal, but for these particular changes, looking at it as it affects the individual may, in fact, be more relevant to what the device actually does during therapy.

DR. HURST: Thank you. Dr. Chugani.

DR. CHUGANI: I think a historical group should be sufficient.

DR. HURST: Dr. Ravina.

DR. RAVINA: I think it's going to be difficult to get -- you want to understand the safety profile long term. I think it's going to be difficult to have any really meaningful comparison long term for these safety issues. I think the best that you can do is get adequate information to have a reasonable estimate of the incidents with some of these side effects with some certainty, narrow enough confidence intervals. That estimate will include both the natural history that would occur without treatment in this cohort as well as the added risk related to the intervention.

DR. HURST: Ms. Peterson.

MS. PETERSON: I concur with Drs. Barker and Ravina.

DR. HURST: Thank you. Mr. Halpin.

MR. HALPIN: I think that in this context, it sounds like exposure to the product and understanding the product better in terms of safety issues seems to be the key. I'm not sure that a comparator is necessary to do that.

DR. HURST: Dr. Nikhar.

DR. NIKHAR: Yeah, it's hard. I don't know if there's a way to make a comparison group possibly between best medical therapy, including the medical plus surgical therapy that's patients have undergone. I don't know how you'd make an active comparison group.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I agree with everything that Dr. Barker said and would add that the quantitative measures of the profile of mood state and cognitive measures did not show a difference between the active and control groups in the trials. So I just don't think you're going to be able to see much in an open label trial like this.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I would agree with Dr. Barker. I would also note that since having a history of depression, cognitive changes is not an exclusionary criteria for getting the device in the future. The patients might actually have more robust reporting of these symptoms pre-implant.

DR. HURST: Thank you. So my sense is that while ideal, an active comparison group would be exceedingly difficult and perhaps even impossible in this case, that we should certainly consider historical data, best medical therapy, other DBS populations, but again extremely difficult. Certainly monitoring of seizure frequency and depressive symptoms would be very important.

MR. MARJENIN: Thank you. Moving now onto the third part of the question. The SUDEP rate was 9.2 deaths per 1,000 person-years in the premarket study with a confidence interval of 1.90 and 26.98. What would be an acceptable threshold for the rate of SUDEP in a post-approval study? Which safety endpoints, in addition to SUDEP, should be evaluated in a post-approval study?

DR. HURST: Dr. Evans.

DR. EVANS: Well, the endpoints that come to mind are again looking for depression and things like that that sort of raise signals in this particular study. I think coming up with an acceptable threshold is going to vary by person. You could try to come up with a maximum acceptable rate and build a study to try to show that you're within acceptable bounds.

However, doing such a study would require enormous sample size, and I think you're probably going to be limited to trying to estimate this rate with an acceptable level of precision, and by precision I mean the width of a confidence interval, and hopefully that's consistent with what you would expect or not alarming.

And I think that may be the best way to think about designing and thinking about estimating rates involved with future trials because it's going to be variation of opinion about what sort of levels of risk are going to be acceptable, but if you take a strategy of estimating event rates with specified level of precision, then you can allow some sort of flexibility in deciding what sort of rates are acceptable, and then interpretation could vary if people want to use different sort of thresholds.

DR. HURST: Thank you. Dr. New.

DR. NEW: The literature review that I did before this meeting suggested that between 5 and 10 deaths per 1,000 patient-years was acceptable in severe refractory epilepsy, which is what this device is targeting. As far as the safety endpoints, I think I agree with Dr. Evans. Points can be hard to reach consensus on that, but certainly looking closely at the items listed in B is going to be important.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: The suicide rate in the general population is under 2 percent. It's closer to 1.5 percent, not including folks with a seizure disorder.

DR. NEW: Oh, sorry. Just to clarify. I wasn't talking about suicide but SUDEP.

DR. PETRUCCI: Okay. And I'm not sure what the confidence interval should be given the population. Perhaps one way of encouraging a better SUDEP rate would be to eliminate those folks that have previously shown susceptibility to either self-harm or sudden experiences of death.

DR. HURST: Thank you. Dr. Engel.

DR. ENGEL: Yeah, I didn't see anything that made me concerned that the device itself increases the risk of SUDEP, and I would have no idea how to go about setting a limit of an acceptable rate of SUDEP.

DR. HURST: Dr. Good.

DR. GOOD: My general sense is that the rate is acceptable, but it needs to continue monitoring in the future.

DR. HURST: Dr. Barker.

DR. BARKER: We saw information that the rate best estimate was the same as in untreated patients and might be as high as 2.5 times that. I think that if you had a more precise estimate, that that could be presented to the patients who are qualified to make their own decision about a therapy that improves quality of life and may have some small risk of death.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: Given that it does match as we mentioned before the incidence that's part of the natural history of this disease, unfortunately as it stands, one would say that that's an acceptable threshold at this time, but certainly there could be some determination of stopping the study if it reached a certain degree that may be unacceptable, i.e. two times that rate. And, obviously, there been no data to suggest that would be the case, but certainly some confidence determinant could be established.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I agree with Dr. Engel. I don't see any connection between SUDEP and the stimulation.

DR. HURST: Dr. Ravina.

DR. RAVINA: Yeah, I think it's similar to the previous question we just answered. So it's an issue of the precision of the confidence interval. It's rare that we ask of trials that they exclude an AE rate of any particular magnitude. So I think it's a difficult issue. You could see an upper limit that you might want to exclude as you narrow that, for example, twofold above that 9.2 or so estimate.

DR. HURST: Thank you. Ms. Peterson.

MS. PETERSON: I'll defer to the clinicians on the Panel.

DR. HURST: Mr. Halpin.

MR. HALPIN: I'll defer as well.

DR. HURST: Dr. Nikhar.

DR. NIKHAR: Yeah, I think as long as it's within the established data for SUDEP and the suicide rate, I think that should be fine, and the data so far suggests that that's the case.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: Yeah, I'm not sure what we would be able to do because they're proposing following 100 patients and then adding another 50. So I'm not sure that we have any way of really saying that SUDEP was increased or not increased unless there was a really dramatic increase in the SUDEP.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: I think that the rate is within the rate we would expect for the population, but it merits ongoing evaluation.

DR. HURST: The general sense appears to be that in general there doesn't seem to be any data that there is an increase in SUDEP rate associated with the evidence so far. While an event rate might be estimated, postmarket monitoring could be instituted, and if an increase in rate over 2 times, say, the 9.2 or so per 1,000 that appears to be in the literature, then that could serve as a warning.

MR. MARJENIN: Thank you. And finally for Part D, the applicant did not propose any subgroup analysis. Please discuss whether the study should include subgroups such as various sites of seizure onset, failed VNS therapy, prior ablation or resection procedures, subjects between the ages of 18 and 21, or any additional subgroups.

DR. HURST: Dr. Evans.

DR. EVANS: I think performing subgroup analyses is informative, and I don't discourage it, although they have to be done carefully, and there's several complications involved. In studies of this size, unless the future studies get much larger, you're not going to have a lot of power to assess treatment effects within subgroups. You're also not going to have a lot of power to determine whether treatment effects vary across subgroups, and looking at interactions as done here is the first step, I think.

There are some more advanced methods or more recent methods dealing with how treatment effects might vary across patient risk subgroups you might say, but it involves essentially for each patient coming up with some sort of risk score which may be a function of their demographics and other baseline characteristics. And the nice thing about that is you eliminate the multiplicity issue associated with all the subgroup analyses, but it still requires some sort of validation, and it's going to be tough to do much validation with the numbers that we're looking at.

So I would not discourage it, but I would caution interpretation of results of subgroup analyses. You're not going to have high power. I would assess interactions first, and with low power, there's a very good chance that interactions may not look significant, in which case you might want to avoid subgroups altogether.

DR. HURST: Thank you. Dr. New.

DR. NEW: I think subgroup analysis would be very helpful, and Dr. Evans, of course, is absolutely correct about the power is really going to be difficult. Of course, the post-approval study is just a proposed study. We can certainly suggest that perhaps the numbers should be a little bit larger, but if I might just ask a clarifying question. Wasn't the plan to have 100 more patients total followed in that or --

DR. EYDELMAN: Again, you're commenting on the ideal design, not on the proposed design.

DR. NEW: Right. Okay. Yeah. So probably a doubling in the size to 100 more patients would be good, which I thought was the proposed design, but subgroups in particular, clinically, that I'm interested in is patients who have had surgical resective surgery, or not, in the past and the age of the patient.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: I think any and all efforts should be made at trying to obtain as much information as we can from very small groups. Trying to identify the site of the lesion, the site of the seizure is I think important for cognition and for affect as well as for other areas of memory disturbance. Identifying those who have failed the VNS is important as well.

And the subjects between the ages of 18 and 21 are sort of curious. That's a very difficult age to maintain command over, given their early adult adjustment and the interruptions that they have with their seizures. So I would make every effort at trying to look at this group.

DR. HURST: Thank you. Dr. Engel.

DR. ENGEL: Yeah, I think subgroup analysis is very important, and even if you're not going to come up with any statistically significant data, you're going to develop hypotheses that can be pursued. In addition to looking at location of the lesion, I think the etiology and the epilepsy syndrome are things that you need to consider.

DR. HURST: Dr. Good.

DR. GOOD: We lost power on this side of the table here. It must be time to quit.

I agree with the comments that have already been made about subgroup analysis.

I just want to throw something else out though. We really haven't heard anything about stimulation settings except three different stimulation settings were used in the unblinded phase. I'm sure somebody's looking at that. Probably the numbers are very small unfortunately, but that's something that certainly has to be looked at in the future. Thanks.

DR. HURST: Dr. Barker.

DR. BARKER: I would say that the device will be used indiscriminately if it's approved and that the best way to find out what groups it works best in would be in the postmarketing study where you would think that data could be generated that could be pooled effectively with the existing trial data.

I would say that the two things that I would add to this list that would be so important that I would want to see an analysis of the existing data would be an analysis of efficacy by number of seizures per month in the baseline period and also by duration of epilepsy before receiving the treatment.

DR. HURST: Thank you. Dr. Paolicchi.

DR. PAOLICCHI: Just to add on comments already made by the Panel, I think in terms of the first analysis, various sites of seizure onset, I think overall that this is less relevant to this population. It's been discussed before. This is a group that has poorly localized seizures. Therefore, they're refractory, and we can assume that they've had poor localization hopefully by previous evaluations. Therefore Dr. Engel's suggestion of etiology and epilepsy syndrome would be far more relevant and important analyzing groups that may have benefit of this procedure.

From a clinical epileptologist perspective, the groups that we would be most interested in using this device on are the failed VNS therapy and the failed resective surgeries. So continuing data analysis of these groups would be most relevant. This is the patient group that we'd most consider the device.

And, lastly, and I want to make this very strong point, that I would strongly advocate to the sponsor, that on ethical and scientific grounds, that they subsidize studies in the pediatric population. This is a group that has a similar rate of refractory epilepsy. They often have inadequate trials and leads to inadequate data to make clinical decisions on new devices, and I would strongly urge them to sponsor trials in this population.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I would like to see a subgroup analysis in terms of lifetime number of seizures, so that would include frequency of seizures plus duration and particularly those with secondary generalization of the seizures because I think those kinds of seizures tend to alter the circuitry much more robustly than without secondary generalization. So I think the composite of those would be important. I tried to get at that issue a little bit this morning.

DR. HURST: Thank you. Dr. Ravina.

DR. RAVINA: Yeah, I think because of the sample size issues, while this is important to look at, it won't necessarily be limited and should be viewed as hypothesis generating. I think it will be most important to look at the kinds of factors that can be adequately quantified up front prior to surgery that may therefore be used to refine the patient population.

DR. HURST: Ms. Peterson.

MS. PETERSON: I'd defer to Dr. Evans and the clinicians on the Panel.

DR. HURST: Mr. Halpin.

MR. HALPIN: From an industry perspective, typically sponsors put draft proposals together for these types of studies, and I'm sure that they're expecting to have negotiations on things like this.

DR. HURST: Dr. Nikhar.

DR. NIKHAR: I think the struggle will be getting a large enough number to have a meaningful subgroup analysis but, you know, I also wondered about the VNS failures. Most of these patients had VNS leads already implanted, and we haven't looked into or there hasn't been a discussion about having the VNS continue and DBS.

DR. HURST: Dr. Privitera.

DR. PRIVITERA: I'd be interested in looking at a subgroup analysis of temporal versus extratemporal with the limitations that we said before, that it's very difficult to actually ascertain exactly where the seizures come from.

I think it would also be important in postmarketing to have some testing designed to identify a depression instrument that clinicians could use so that neurologists who are notoriously bad at asking questions about depression could look at that.

I don't see a great value in any of the other subgroup analyses on the screen.

DR. HURST: Dr. Jacobson.

DR. JACOBSON: Although the sample size may be so small that, you know, ideas of subgroup analysis might be like making a Christmas wish list, but I think it would be important to identify who the non-responders are, to try and characterize them because if we could do that, then you'd focus on who benefits and for others avoid implantation for people who would be waiting a very, very long time before they ever got benefit.

DR. HURST: Yes, Dr. Engel.

DR. ENGEL: One more comment on the PAS, which hasn't been mentioned, is that I note that you did a Liverpool Severity Scale, but I didn't see much in there about it, and the anecdotal testaments that we heard suggested that seizures are much less severe. So I would hope any PAS would include more detailed information about seizure severity.

DR. HURST: Thank you. Yes, Dr. Eydelman.

DR. EYDELMAN: Just a comment back on Dr. Nikhar's point. I just wanted to clarify that any post-approval study can only be designed to study an approved indication.

DR. HURST: So my sense is that the Panel does feel that subgroup analysis would be useful and informative and very helpful but may require larger studies or you might not have sufficient power to look at the treatment effects in subgroups. Subgroups that might be useful would include the ones listed here, including failed VNS therapy, as well as those patients who might have failed resection, the age group 18 to 21, by number of seizures per month, by seizures that are secondarily generalized, by duration of seizure disorder, by various syndromes in the pediatric population, associated with some depression testing instrument that might be instituted, non-responders, and stimulation settings.

Was that sufficient?

DR. EYDELMAN: Thank you very much.

MR. MARJENIN: Thank you. And that concludes the Panel questions.

DR. HURST: Are there any final comments or clarification from FDA, Mr. Marjenin, or Dr. Eydelman?

DR. EYDELMAN: Yes, actually I would like to ask Mr. Marjenin to present our summation slides if he has that with him.

DR. HURST: Thank you.

MR. MARJENIN: First of all, I would like to thank the Panel members and the members of Medtronic for an excellent discussion today, and at this time, I'd just like to give several brief summary comments.

First of all, the GEE model was selected to address the inherent variability of the seizure counts, and comparing a single month of data to the three-month baseline data we believe is questionable.

Overall median total seizure frequency, I believe, is a point that came up earlier. In looking at the percent change from baseline, if you're looking at the overall changes in the active group, you see a 35 percent reduction. In the control group, you only see a 21.1 percent reduction. The difference between the two groups then is about 14 percent.

And the individual response has been provided on the second slide on page 23. There was a comparison of the responder rates, and there were no differences, and as Mr. Van Orden mentioned, there was no difference even if the cutoff was changed to less than 50 percent, and this is just to reiterate that slide.

In the 110 implanted subjects, there were 808 adverse events in 99.1 percent of the subjects and 55 serious adverse events in 36.4 percent of the subjects during the operative through unblinded phases of the study.

And as we've mentioned, there were a total of five deaths in the implanted subjects, and three of these were determined to be SUDEP, one was a suicide, and the cause of the recent death is currently unknown.

There were seven suicidality events in addition to the suicide, and in addition, more subjects in the active group than the control group reported depression, anxiety, and memory impairment events.

Now, the differences in the injury-related adverse events between the active and control groups was due primarily to an increase in the rate of these events in the control group as opposed to a decrease in the injury events in the active group, and therefore the difference between the two groups in the blinded phase may not necessarily be related to the device effectiveness.

FDA believes that the data from the study should demonstrate both statistical and clinical significance, and we ask that you consider both in your final vote.

To summarize the effectiveness, the study failed its primary effectiveness endpoint as well as the secondary effectiveness endpoints. All of the additional study measures, such as the seizure type and quality of life, also had p-values that were greater than 0.05. And I would just like to remind you that the analyses of the most severe seizures and the seizure-related injury were exploratory, and the study was not powered to adequately assess them.

Also using the three to four month data on its own in order to establish device effectiveness is questionable due to the fact that there is such a wide variability in the monthly seizure counts.

And, finally, the data from the unblinded and long-term follow-up phases may be confounded by such factors as unblinding, the fact that subjects could change their antiepileptic drugs. They could also change their stimulation settings, and there's also missing data.

And with that, I'm going to conclude and would just like to thank you again for a very productive discussion today.

DR. HURST: Thank you, Mr. Marjenin. Is there any final comment or clarification from the sponsor?

DR. FISHER: This is my first Panel, and I'm extremely impressed at how much detail the Panel absorbed about this trial, which I know you haven't had that long to look at, and how much thoughtfulness goes into this.

Now, we agree with the FDA on three points. We agree that the GEE analysis, which is basically a relative of ANOVA with repeated measures, is the best statistic to use because it takes into account the many factors that the Panel has been considering, such as the variation and seizure frequency, the possible effect over time, which was significant. I heard that it was not significant, but it was significant according to our specified levels and also considers seizure counts as a ratio. So that's point one of agreement. We agree that the GEE is the most all encompassing, unbiased methodology.

Secondly, we agree with the FDA that Subject A, Troy, he has a name now, was an outlier and that Subject B was not an outlier. That was said in the presentation. And, in fact, Subject B is a bit of a distraction because he's a point of discussion since he started having pseudoseizures during the day at nine months into the trial, which are not relevant to his nocturnal seizures in the blinded phase. He didn't have those in the blinded phase.

Third and most importantly, we agree with the FDA that we met statistical significance over the course of the entire blinded phase, not just month 3 to 4, the entire blinded phase, if you discard the data from the outlier. There's no disagreement about that. As a matter of fact, there was discussion of alternative analysis in the presentation. There were also several versions in your packet material, but it seems to have disappeared from discussion and the Panel now.

In fact, what it really means is that you have this one patient who is an outlier, not because he had so many seizures that we were afraid he was going to spoil the data, but because he had a seizure every 6 minutes when the stimulator was turned on, and that's a different type of seizure from the type that we are treating, not to mention that he had a 1300 percent increase in seizures. So we worry, my goodness, the study is not robust because data from one patient can skew it.

Well, if you throw a patient with a 1300-fold seizure frequency in a study of valproic acid for generalized seizures, you will probably not have trouble obliterating significance. So as you say, you've got to look deeper. It depends upon what the nature of that data are, and you just can't consider any one p-value or any one point in isolation.

Now, much also has been discussed about the median differences, subtracting the median differences, numbers such as 2.2, 2.5. I happen to think that you have to add the 3.3 treatment defect to that, and then you're talking about numbers 5.8, but that's not really the point. The point is that the median differences were never prespecified in our protocol, and the reason we didn't prespecify them is because they're not particularly clinically relevant. The relevant number are percentage improvements, which at the end of the blinded phase was 40 percent, and in the GEE analysis was

29 percent active over control. Is that correct, Dr. Rochon?

So those are the meaningful clinical differences, and they are meaningful.

We didn't do particularly well on responder rate. As Dr. Privitera suggested, on the other additional study measures, we rolled the dice to see if they would be --

DR. HURST: Excuse me, Dr. Fisher. You have about 30 seconds left.

DR. FISHER: Okay. On suicidality, I would suggest the rate is 7.6. The woman drowning in a bathtub was possible.

The device is reversible. It's been used in over 70,000 patients. We do have additional support in severity with complex partial seizures, with reduced seizure severity.

It may be tempting to suggest another trial, randomized. That would delay for five years, and speaking now not as a Medtronic representative, which I'm not, but as a treating physician, I hope my patients don't have to wait five years, and I hope that these issues can be handled by some very judicious postmarketing questions because I feel that there's good reason to say that we have efficacy and, in this intractable population, we have safety.

DR. HURST: Thank you, Dr. Fisher.

DR. FISHER: Thank you.

DR. PAOLICCHI: Can I ask one question? I think you mentioned suicidality, and I think you meant SUDEP. Is that correct? The woman drowning in the bathtub.

DR. FISHER: Yes, I'm very sorry. That was SUDEP. Suicidality, the rate was greater per time in the baseline than in the stimulated section.

DR. HURST: Before we proceed to the vote, I'd like to ask Ms. Carolyn Peterson, our Consumer Representative, and Mr. Michael Halpin, our Industry Representative, if they have any additional comments? Ms. Peterson.

MS. PETERSON: Thank you, Dr. Hurst. First, I'd like to commend our patients who come to speak today, Troy and Jennifer Gibson, Shannon and Jackie, and Tina and her mother. It's particularly difficult when we have data that doesn't give us a clear direction or guidance for interpretation to hear from our patients and to get their perspective about what that means to be in a trial and to have the opportunity to use a device.

I think you heard perhaps from some of the Panelists today, this is one of the most challenging, if not the most challenging Panel that many of us have been on, and it's very, very helpful to hear from the patients and to see the face of the work that we're all trying to do.

Second, I'd like to commend my co-Panelists for your diligence and your efforts in going through all the data and bringing up so many issues and for so vigorously debating the 14 questions that we had today which I think is a record at least for all the Panels that I've been on. It's a long day, and you've shown enthusiasm and interest in working through all the issues.

With that said, I respectfully suggest and hope that you will continue in your deliberations to find a way that we can continue to research this device with the goal of determining the appropriate patient population and usage so that some other patients with refractory epilepsy can benefit from it.

DR. HURST: Thank you, Ms. Peterson.

Mr. Halpin, do you have any comments?

MR. HALPIN: Yes, I'd also like to thank the sponsor, the FDA, the Panel, as well as the visitors today that spoke. I think this was a very enlightening meeting.

In closing, I would just like to state and reiterate the sponsor's summary that if you look at the blinded phase, you remove Subject A, what you actually see is an overall statistically significant difference for that entire blinded phase, and that you're actually comparing a control arm which is part of the treatment device. That's it. Thank you.

DR. HURST: Thank you. Ms. Falls will now read some very important material into the record.

MS. FALLS: For the record, Drs. Barker, Paolicchi, and Chugani have been granted temporary membership to the Neurological Devices Panel and authorized to vote by Jill Warner, Associate Commissioner for Special

Medical Programs. Thank you.

DR. HURST: I'll remind the Industry and Consumer Representatives that they will not vote and that the Chairman of the Panel will vote only if there is a tie among the Panel members.

With respect to our voting instructions, we're now ready to vote on the Panel's recommendation to FDA for this PMA. Panel members, please refer to the voting options flowchart in your folder.

Ms. Falls will now read the Panel Recommendation Options for premarket approval applications.

MS. FALLS: Thank you. The Medical Device Amendments to the Federal Food, Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device premarket approval applications that are filed with the Agency. The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable, publicly available information.

The definitions of safety, effectiveness, and valid scientific evidence are as follows:

Safety, 21 C.F.R. Section 860.7(d)(1) - There is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

Effectiveness, 21 C.F.R. Section 860.7(e)(1) - There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Valid scientific evidence, 21 C.F.R. Section 806.7(c)(2) - Valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of safety and effectiveness of a device under its conditions of use. Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence to show safety or effectiveness.

Your recommendation options for the vote are as follows:

1. APPROVAL - If there are no conditions attached.

2. APPROVABLE with conditions - The Panel may recommend

that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or a further analysis of existing data. Prior to voting, all of the conditions should be discussed by the Panel.

3. NOT APPROVABLE - The Panel may recommend that the PMA is not approvable if:

- the data do not provide a reasonable assurance that the device is safe or

- the data do not provide a reasonable assurance that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, Dr. Hurst will ask each Panel member to present a brief statement outlining the reasons for his or her vote. Dr. Hurst.

DR. HURST: Panel, please refer to the voting procedures chart in your folder. Are there any questions from anyone on the Panel about these voting options before I ask for a motion on the approvability of this PMA? Dr. Paolicchi.

DR. PAOLICCHI: If the Panel votes for approvable with conditions, does that mean that the device is available then to the public or only prior to the conditions being met? And how does the FDA establish whether those conditions are being met?

DR. HURST: Dr. Eydelman.

DR. EYDELMAN: Approvable with conditions implies that the device will not be approved until all of the conditions are met. It is up to the Panel as to how much information you would like to provide us as to what you would find adequate completion of those conditions. The more recommendations you provide, the better off we usually are.

DR. PAOLICCHI: I'm sorry. What was your last point?

DR. EYDELMAN: The more specific you would like to be, the better off everybody is.

DR. PAOLICCHI: And it's a democratic vote, and the Chairman has the tie. Is that correct?

DR. HURST: Only if there's a tie do I vote, yes. Yes, Dr. Good.

DR. GOOD: One other point. This is an Advisory Committee to the FDA, right?

DR. HURST: Yes.

DR. EYDELMAN: Yes, it is.

DR. HURST: Any other questions?

Then is there a motion for either approval, approvable with conditions, or not approvable from the Panel? Dr. Engel.

DR. ENGEL: I move that we consider this device approvable with conditions.

DR. HURST: Is there a second for the motion?

UNIDENTIFIED SPEAKER: Second.

DR. HURST: Is there any discussion on the motion?

DR. BARKER: What conditions?

DR. HURST: It has been moved that the PMA be approved with conditions. Please refer to the yellow portion of the voting procedure flowchart in your folder.

Remember, we are voting on the conditions of approval for this PMA application as it stands. We must first recommend a condition. The condition must then be seconded. There will be a discussion regarding the recommended condition as it was worded. There will then be a vote on that condition. If that condition is approved, it will be the first condition to the main motion, approvable with conditions. We will then move onto a new condition and repeat this process until there are no new conditions.

Finally, we will vote on the motion to approve the Medtronic DBS System with all of the conditions we have just approved by a majority vote.

Questions? Does anyone wish to recommend a condition? Dr. Engel.

DR. ENGEL: Can I recommend a condition that just states that there be labeling as we discussed, or do we have to go through all the labeling?

DR. EYDELMAN: It would be helpful if you just delineate the key aspects.

DR. ENGEL: Well, the key aspects for labeling with regards to depression and SUDEP and anxiety and memory were all pretty much discussed before.

DR. JACOBSON: And could we add suicidality specifically as well.

DR. ENGEL: Post-suicidality and depression and increased seizures.

DR. NEW: Right. No warning for SUDEP, right, because we don't think that increases.

DR. ENGEL: That's right. We decided SUDEP was not a warning. Depression, increased seizures, memory, anxiety --

DR. NEW: Suicidality.

DR. ENGEL: -- and suicidality as part of the depression.

DR. NEW: And labeling changes, I'm not familiar enough with the technical terms, does that include the patient therapy manual changes that we talked about as well regarding those things?

DR. EYDELMAN: Yes.

DR. NEW: Thank you. Then I second the motion.

DR. HURST: Okay. So the motion has been made and seconded. Any additional discussion?

Yes, Dr. Ravina.

DR. RAVINA: I'm not sure if this makes sense procedurally, but I really don't believe that efficacy has been shown reasonably, and I can't -- so this does not at all address my concerns. They're far beyond labeling issues, and conditions aside from the second trial wouldn't address my main concerns.

DR. HURST: Okay. Yes, Dr. Privitera.

DR. PRIVITERA: I think that -- I'm not sure that there was an absolute consensus on the issue of memory in the labeling. I think depression was clear. I think the question of suicidality and the increased seizure frequency, but maybe we need to have a little bit more discussion around the issue of memory because the only thing that I heard was that patients complained of memory problems, but we had no objective documentation on neuropsychological testing of patients who had serious or persistent or otherwise intractable memory problems, and I'm not sure that that would deserve a space in labeling as a warning.

DR. GOOD: David Good. But I would add that there was really no evidence for depression in terms of objective testing either, and yet people felt more depressed. So it would seem to me that though memory is a subjective complaint, it ought to be added even there was no objective change.

DR. PRIVITERA: But on the depression side, we had people that were suicidal and people who completed suicide, but I'm just -- I mean the memory, you know, a lot of people who get on various treatments and it's a common complaint and people with epilepsy, and I just didn't get a sense that memory was there. I just didn't get a sense that memory has risen to the level of a warning.

DR. HURST: Yes, Dr. Eydelman.

DR. EYDELMAN: If I can just make a statement in light of the comment that was just made previously. I just wanted to clarify that designing a new trial is not consistent with approvable with conditions. And anybody who around the table is not in agreement with the original motion should not be voting as positive on each one of the conditions because then we're just going to go around in a loop-d-loop. Did that clarify it?

DR. RAVINA: So we should refrain from discussion of conditions if we don't agree with the motion?

DR. HURST: Should they not vote on it at all or vote against it?

DR. EYDELMAN: Against it.

DR. HURST: Against it. All right. So we currently have labeling indications.

DR. PAOLICCHI: I have a procedural complaint with that approach because many of the Panel members may want to voice concerns regarding approvability, but if the overwhelming view of the Panel is to proceed with approvable conditions, they do not want to lose their voice in that matter, and if I'm only speaking for me, that's fine, but that's how I would like to address that issue procedurally.

DR. EYDELMAN: And I think as Dr. Hurst calls on you, you'll have your opportunity to voice your opinion, in addition to vote. This is your opportunity to comment on your opinion.

DR. PAOLICCHI: But you're saying if you're not going to vote for approvable with conditions, you are asked not to participate in the debate on the conditions. That seems to be a problem.

UNIDENTIFIED SPEAKER: But you're going to be asked for your opinion when they go around.

MS. WOODS: Hi. I'm Geretta Woods. I'm the Director of the Advisory Committee Program for CDRH.

First of all, I'd like to say that we will have a full discussion and vote on the conditions. If you disagree with the main motion, you may still vote on the condition so that your voice is heard on those particular conditions. If you feel that strongly that you feel the need to vote against the condition, that's fine, but I suggest that you have your voice heard when it comes to the vote on these conditions. I'm sorry if there was any confusion.

DR. PAOLICCHI: Thank you.

MS. WOODS: Thank you.

DR. HURST: All right. So further discussion on the labeling?

Then we'll now vote on that condition. All in favor of the condition, please raise your hand.

All opposed.

Any abstentions?

All right. I will note for the record that it's unanimous approval.

Is there a motion for another condition?

DR. ENGEL: Can I ask a procedural question?

DR. HURST: Yes.

DR. ENGEL: If we make a condition that there be post-approval studies and want to make sure that the post-approval studies don't hold up the availability of the device now, so that we're not really proposing additional randomized control trials that it be considered unapprovable, how do we do that?

DR. HURST: Yes, Dr. Eydelman.

DR. EYDELMAN: In order for a device to be approvable, an outline of a post-approval study has to be agreed upon between the FDA and the sponsor. The trial itself does not begin until after the device is available on the market.

DR. ENGEL: So can we propose as a condition that there be post-approval studies again along the lines that we discussed?

DR. EYDELMAN: Yes.

DR. PAOLICCHI: Again, I'm so sorry, but I do have another procedural question. It seems like what you just said, Doctor, contradicted what Dr. Hurst said earlier. So you said that if we vote for approvable with conditions, that those will occur after the device is available?

DR. EYDELMAN: No. I was only commenting on the post-approval study. So if one of the conditions of approval is conduct of a post-approval study, post-approval implies it occurs after the approval. So the condition would be that the design of the study and all the other variables are agreed upon prior to the approval. However, the study alone, the study itself will take place after the approval. This is in contrast to all other typical approvability, other conditions which are usually associated with being approvable.

DR. HURST: Dr. Barker.

DR. BARKER: As I understand it, you told us that we can require that there be a post-approval study but that that study can't be intended to prove efficacy.

DR. EYDELMAN: Correct.

DR. BARKER: Are there other restrictions on what a post-approval study may not require?

DR. EYDELMAN: Let me turn it the other way around. The approvability, your approvability of a recommendation should be based on the data that is available today so that the PMA data needs to establish on its own reasonable safety and effectiveness of the device in question.

DR. BARKER: Can you give me an example of what the post-approval study might mandate or require?

DR. EYDELMAN: And, again, this goes back I believe if you open to slide -- there's a slide actually delineating what the typical post-approval studies do, and one of the examples would be to assess how the device performs when it's released to a larger population, to a larger end, and if one of my colleagues can direct me to the slide number. The last two pages, and --

MS. KRULEWITCH: Hi, I'm Cara Krulewitch, Team Leader in the Division of Epidemiology.

Just one other point. In Dr. Soldani's presentation, you'll see that there was a table also that outlined the proposal that the sponsor has given us. We are asking you your opinion of that proposal as well and whether you feel there are other things, including hypotheses, et cetera, as Dr. Soldani pointed out when we developed the post-approval study. We will be working with the sponsor to develop that. So we're asking you those questions.

DR. EYDELMAN: And the slide is on page 28 and 29.

DR. BARKER: Can we mandate that a post-approval study contain a comparator group?

DR. EYDELMAN: Yes.

DR. BARKER: Can it be mandated to be randomized?

DR. EYDELMAN: Yes.

DR. BARKER: How does that differ from mandating a new trial?

DR. EYDELMAN: Okay. Once again, what -- let me try to clarify it. The distinction is the question before you is to decide whether a new trial is needed before you feel that you can make a decision about the reasonable safety and effectiveness of the device prior to its approval. The data collected in a post-approval study is supplemental. In other words, once you have reached the threshold of comfort, that the risk/benefit is acceptable for this device, the post-approval studies are only aimed to give you the additional comfort level.

The plan to conduct the PAS does not decrease the threshold of evidence required to find the device approvable, which is what I just said. The premarket data submitted to the Agency and discussed today must stand on their own at demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable, and general principles -- again, I'm going basically back to the slides. So I can read the slides or I can try to explain it. Either way.

Is there still some confusion?

DR. GOOD: Yeah. When you look at page 29, the bottom of the FDA report, essentially you're asking for study questions, hypotheses, sample size, statistical data analysis, and that almost smells like a whole new trial, you know. So I guess a little clarification might be useful.

DR. EYDELMAN: Okay. So again I think for post-approval studies, the object is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after the premarket establishment of reasonable assurance of device safety and effectiveness. Post-approval studies should not be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

Again, the key distinction that I think is getting lost is whether you feel that the new trial is needed before you feel that the reasonable assurance of device safety and effectiveness has been demonstrated to the point where it can be approvable, versus whether you have additional issues and I think you have to look to clarify further.

DR. LUKE: Okay. My name is Markham Luke. I'm the Chief Medical Officer and Clinical Deputy for Office of Device Evaluation.

With regards to a post-approval study, a post-approval study is not a panacea for data that you need to recommend an approval decision for the medical product or a new indication for a medical product, as is the case where we're discussing today.

As you deliberate, we would like to hear if you think, if you are voting for an approval with conditions, that you're saying the product can go out on the market, what metrics do we need to look at while the product is on the market to keep an observation on that product as it is being used by the general public, those patients, and so that we can continue to monitor safety for those patients and -- safety, but we do build into long-term effectiveness because clinical studies as you heard, during the presentations, it went up to maybe three years at most in a few patients, but what happens to those patients longer than that, and patients' life spans are longer than those three years we hope.

And so we do want to hear from you with regards to what you think in that, and if you're of the opinion that the product cannot be approved unless you need another clinical study, then that's something that you need to look at the other part of that voting schema and address that appropriately and not go the approval with conditions. Yes.

DR. PAOLICCHI: May I respectfully submit to the Chairman, as I'm hearing from this procedural discussion, that the primary vote be on whether it should be not approved or approved based on the data, and once we have the consensus of the Panel, it seems like we can more easily move forward on the conditions. So rather than debating conditions, what I'm hearing from the FDA is we should establish within the Panel whether we're ready to move forward or not.

DR. HURST: I see that you're saying. Let me just ask Dr. Eydelman if that's acceptable because I would agree with you, if you're in a position where your first choice would be not approvable, then you may be in a position of voting for a lot of conditions that you really don't go along with anyway, but let me just ask her if that's an acceptable way to do that or whether we should do it this way. Let's also keep in mind that the motion was made for approvable with conditions, rather than not approvable.

DR. GOOD: A point of reference here. We never voted on that. So he could easily withdraw his motion --

DR. HURST: Okay.

DR. GOOD: -- and then we could have a new motion to approve.

MS. WOODS: Hi. Let me try again to clarify this. We have the motion on the floor. The motion is for approvable with conditions, and I believe those of you I trained yesterday fully understand the process. Some of you who were trained previously may have forgotten, and let me just refresh your memory.

Right now, we can't vote on that main motion until we know what the conditions are. So we're discussing the conditions and voting on them. We must complete this process before we can ask for another motion to be put on the floor. So right now, someone has moved for a condition of approval study. I don't recall if we got a second. If we did not, we need one. And then if you want to talk about how it should be designed in your discussion, that can be added to the condition. Then a vote needs to be taken on that condition, and we will go from one condition to another until you are finished, and then Mr. Chairman will take us through a vote on the main motion, which has been amended with the conditions that you voted on.

Now, I know it's painful, but we have to go through that process.

DR. EYDELMAN: Can I just add, while you're still at the podium, unless somebody wants to withdraw the motion on the table and propose an alternative motion, correct?

MS. WOODS: Well, you're going to have to -- any condition that's been voted on would have to be withdrawn first. So we're in it, let's continue on.

DR. ENGEL: Can I clarify the motion, the second motion, the third motion that I made, which was the condition that there be post-approval studies, that these post-approval studies be for the safety purposes that we have already discussed to follow patients to see if we can identify risk factors for depression, suicide, increased seizures, to see what the risks actually are, that we look for subgroup analysis to see if we can figure out what predictive factors there are, and that there be a comparison group to be determined between the sponsor and FDA, or comparison groups, depending on the questions.

DR. HURST: Is there a second to that motion?

UNIDENTIFIED SPEAKER: I'll second it.

DR. HURST: Okay. A motion has been made and seconded. Discussion.

DR. JACOBSON: Could I add a condition?

DR. HURST: We have to vote on this condition, I believe, right?

DR. EYDELMAN: Discuss it and vote on it.

DR. HURST: Okay. Any discussion?

DR. PRIVITERA: Yes. I don't believe that we need a comparison group.

DR. HURST: Okay. Any other discussion?

DR. BARKER: I believe there should be a comparison group.

DR. HURST: Okay. We can vote on it. All right. All in favor of the motion?

DR. NEW: Can I clarify about this comparison group? So you're saying a comparison group other than just the patients followed at baseline first.

DR. ENGEL: It could be a historical comparison group. It doesn't have to be --

UNIDENTIFIED SPEAKER: That's not --

DR. ENGEL: Yeah, sure, historical controls are a comparison group.

DR. HURST: All in favor of the motion?

DR. PAOLICCHI: Clarify what motion we're voting on.

DR. HURST: That there should be a control group.

MS. WOODS: James, go ahead and take the mic and restate the motion if you have it written down, please.

DR. ENGEL: I'll restate the motion again. That there be post-approval studies to further assess predictive values of looking at subgroups and risk factors for the safety issues that we discussed and that the issue of a comparison group, that there should be a comparison group, and I'll state which could be historical controls should be left up to the sponsor and the FDA to discuss, depending on the question. I mean some of these questions may need a comparator; some may not.

DR. HURST: All in favor? Okay. State your names, please go around, those of you who are in favor.

DR. CHUGANI: Harry Chugani.

DR. PAOLICCHI: Julian Paolicchi.

DR. BARKER: Fred Barker, I vote yes.

DR. GOOD: David Good.

DR. ENGEL: Pete Engel.

DR. PETRUCCI: Ralph Petrucci, yes.

DR. NEW: Kent New, yes.

DR. JACOBSON: Mercedes Jacobson, yes.

DR. PRIVITERA: I'm going to vote no. Are you going through the yeses, or do you want a name and a vote?

DR. HURST: We're just voting for the yes right now, I believe.

DR. NIKHAR: Nirjal Nikhar, yes.

DR. HURST: Okay. The motion has been carried. Okay. Everybody opposed, all opposed?

Two. State your name, please.

DR. RAVINA: Bernard Ravina.

DR. PRIVITERA: Michael Privitera.

DR. HURST: Thank you. So the motion has been carried. Is there a third motion?

DR. GOOD: I would like to make a motion. I would like to add that any of the post-approval studies be hypothesis driven.

DR. HURST: Is there a second to that?

UNIDENTIFIED SPEAKER: I'll second it.

DR. HURST: The motion has been made and seconded. Any post-approval studies be hypothesis driven. Discussion. No discussion.

DR. ENGEL: I would like to discuss that. I think given the size of these studies, it's going to be very hard to make them hypothesis driven. They're really designed to create hypotheses, not to prove hypotheses.

DR. RAVINA: Just to say, I think only motions that have some real specificity are going to be useful.

DR. PAOLICCHI: I concur, and given even the safety labeling, hypothesis could be driven such as, number one, there isn't an increase rate of SUDEP over 9 per 1,000 patients, and that could be evaluated; number two, the risk of suicidality can be measured in a certain population; number three, screening for depression may be more adequately determined in this population using the various qualities or the various screening techniques that are chosen by the FDA and sponsor; and number four, I think I'm on, there can be stimulus-induced seizures seen in the initiation of the device that will be monitored and again, my recommendation previously had -- that can be monitored, and that can be discretion between the FDA and the sponsor, but an EEG would be recommended.

So those are all ideas for hypothesis driven, and the fourth, I think, or the fifth by Dr. Good earlier would be some testing of the appropriate parameters that are most efficacious for patients as well as tolerable.

DR. ENGEL: So clarification. Are you saying they should all be hypothesis driven or just that some of them could be?

DR. GOOD: No, I think that any postmarketing studies ought to be hypothesis driven. I don't think that the material that goes in the patient education material needs to be hypothesis driven. I'm only talking about postmarketing studies per se, and I don't think I have to propose individual hypotheses for those.

DR. HURST: Other discussion.

If no further discussion, all in favor.

DR. EYDELMAN: Can you please restate the motion before you vote on the motion?

DR. HURST: Yes.

DR. GOOD: I move that any postmarketing studies that are negotiated between the FDA and the sponsor be hypothesis driven.

DR. HURST: All in favor? Please state your name beginning here, please.

DR. CHUGANI: Harry Chugani, yes.

DR. PAOLICCHI: Dr. Julian Paolicchi, yes.

DR. GOOD: David Good, yes.

DR. BARKER: Fred Barker, yes.

DR. NEW: Kent New, yes.

DR. PRIVITERA: Michael Privitera.

DR. NIKHAR: Nirjal Nikhar, yes.

DR. HURST: All opposed? State your name, please.

DR. ENGEL: Pete Engel, no.

DR. PETRUCCI: Ralph Petrucci, no.

DR. JACOBSON: Mercedes Jacobson, no.

DR. HURST: Any exceptions or abstentions?

DR. RAVINA: Bernard Ravina, no.

DR. HURST: The motion has been carried.

Is there a motion for another condition?

DR. JACOBSON: Can I propose a motion for another condition?

DR. HURST: Yes.

DR. JACOBSON: There should be a pregnancy registry to keep track of pregnancy outcomes because there would be pregnancies in women who get the stimulator implanted, unless there's a contraindication, right, once it's approved?

DR. EYDELMAN: I guess I just wanted to clarify. You're recommending that there be a registry in addition to a post-approval study?

DR. JACOBSON: No, the sponsor collects outcomes, right, keeps track in the study.

DR. EYDELMAN: So that that be an additional condition of approval of a registry in addition to a post-approval study?

DR. JACOBSON: Yeah, that would be ideal, that they actually have a pregnancy registry in addition to the post-approval study. So even women who don't participate in the post-approval study who get the stimulator who have pregnancies would still be monitored.

DR. EYDELMAN: Okay.

DR. JACOBSON: It might be a very small number, but we haven't heard.

DR. HURST: The motion has been made. Is there a second?

There's no second. The motion fails.

Is there another motion, a motion for another condition?

DR. GOOD: I have one more motion. I would suggest that any postmarketing studies have adequate follow-up up to five years.

DR. HURST: Is there a second for that motion?

UNIDENTIFIED SPEAKER: Second.

DR. HURST: There is a second. Discussion?

All right. We'll vote on it. All in favor? State your name, please.

DR. CHUGANI: Harry Chugani.

DR. PAOLICCHI: Julian Paolicchi.

DR. BARKER: Fred Barker.

DR. GOOD: David Good.

DR. ENGEL: Pete Engel.

DR. PETRUCCI: Ralph Petrucci.

DR. NEW: Kent New.

DR. JACOBSON: Mercedes Jacobson.

DR. PRIVITERA: Michael Privitera.

DR. NIKHAR: Nirjal Nikhar.

DR. HURST: All opposed?

Abstentions? State your name, please.

DR. RAVINA: Bernard Ravina.

DR. HURST: The motion is carried.

Is there a motion for another condition?

DR. PAOLICCHI: Formulating it. I make a motion that postmarketing studies actively involve either neuropsychology or psychiatry in order to determine the best screening and follow-up tools for depression and suicidality in the studies.

DR. HURST: Is there a second?

DR. PETRUCCI: Second.

DR. HURST: The motion has been made and seconded. Discussion?

All right. All in favor? State your name, please.

DR. CHUGANI: Harry Chugani.

DR. PAOLICCHI: Julian Paolicchi.

DR. GOOD: David Good.

DR. BARKER: Fred Barker.

DR. ENGEL: Pete Engel.

DR. PETRUCCI: Ralph Petrucci.

DR. NEW: Kent New.

DR. JACOBSON: Mercedes Jacobson.

DR. NIKHAR: Nirjal Nikhar, yes.

DR. HURST: All opposed?

Abstentions? State your name, please.

DR. PRIVITERA: Michael Privitera.

DR. RAVINA: Bernard Ravina.

DR. HURST: The motion has been carried.

Is there a motion for another condition?

DR. CHUGANI: I just want to ask, can we make a motion that there be trials in children?

DR. HURST: I don't see why not.

UNIDENTIFIED SPEAKER: Isn't that a new indication?

DR. HURST: It's a new indication.

DR. EYDELMAN: Yes, you cannot ask for post-approval study on a not-approved indication, which is what I've stated before.

DR. HURST: So the answer is no then. Is that correct? We cannot ask for trials in children.

DR. CHUGANI: So that has to be a separate submission.

UNIDENTIFIED SPEAKER: That would be a new PMA.

DR. HURST: Correct, a new PMA.

DR. PAOLICCHI: Again, may I reiterate my comment to the sponsor, that I feel that's ethically and scientifically something that should be done. Thank you.

DR. HURST: All right. So we can vote on the overall motion?

DR. EYDELMAN: If I can just clarify, I'm sorry, to go back. 18 to 21 is considered children. So you can't -- if you wanted to study those three years of age, that's the only thing you could require was in the pediatric.

DR. PAOLICCHI: I would respectfully disagree, as would all 18- to 21-year-olds.

DR. EYDELMAN: This is the legal definition, not necessarily maternal.

DR. CHUGANI: I just wanted to make the point and go on record that the effects of seizures, particularly uncontrolled seizures, is much more devastating in children than they are in adults, and it is with the kind of a feeling that I ask for this kind of indication but, you know, the rules are the rules.

DR. EYDELMAN: But the proposed indication on the table is for 18 and above.

DR. LUKE: On the pediatric issue, I think we hear your concern, and it is on the record, and our transcript will reflect that. Thank you very much, and FDA is in agreement with regards to pediatric development for devices is an important area for future consideration. Thank you.

DR. GOOD: Point of clarification. There is a motion on the table to approve 18 to 21. Is that correct? That would be for both the device as well as any postmarketing studies?

DR. HURST: I don't believe there is a motion.

DR. EYDELMAN: The proposed indication as was read previously is for 18 and above. From what I heard, there was no motion from the Panel to limit that proposed indication. If that is what you -- okay.

DR. HURST: So there is no motion. Any other conditions?

All right. Then it's been moved and seconded that the PMA 960009 for Medtronic Incorporated Deep Brain Stimulation System for Epilepsy be found approvable with five conditions the Panel has just approved.

We will now vote on the main motion. With a show of hands, please indicate if you concur with the recommendation that the above-named PMA be found approvable with conditions. And please state your name.

DR. CHUGANI: Harry Chugani, approve.

DR. BARKER: Fred Barker, approve.

DR. ENGEL: Pete Engel.

DR. PETRUCCI: Ralph Petrucci, approve.

DR. NEW: Kent New, approve.

DR. JACOBSON: Mercedes Jacobson, approve.

DR. PRIVITERA: Michael Privitera.

DR. HURST: All opposed? And please state your name.

DR. RAVINA: Bernard Ravina.

DR. PAOLICCHI: Julian Paolicchi.

DR. GOOD: David Good.

DR. EVANS: Scott Evans.

DR. NIKHAR: Nirjal Nikhar.

DR. HURST: And the motion is carried.

And no one was abstaining.

So it's the recommendation of the Panel to the FDA that PMA 960009 for the Medtronic DBS System be found approvable with the stated conditions.

I will now ask each Panel member to state the reasons for his or her vote, starting with Dr. Nikhar.

DR. NIKHAR: So the essence of this discussion was whether the data presented has been robust enough to consider the risk/benefit in favor of this procedure or not. From the data presented today, I think there was considerable controversy whether it is or not, and I'm not convinced that the data is robust enough to prove that assertion, that it is at least at this time both safe and efficacious, although the trend is promising. So I voted no.

DR. HURST: Thank you. Dr. Privitera.

DR. PRIVITERA: I believe that the analysis with the elimination of the outlier, Subject A, allowed a positive primary outcome, and I believe that the data presented on safety are adequate.

DR. HURST: Thank you. Dr. Jacobson.

DR. JACOBSON: With the elimination of the outlier, I believe that this is a safe and effective device for a very intractable patient population.

DR. HURST: Dr. Evans.

DR. EVANS: I voted no. I come back to the phrase of reasonable assurance, and I never reached that level of assurance. This is not necessarily due to the one patient for the questions about p-value significance or non-significance. When there's a close call and a tough decision to be made, then I guess what I do is I look at other issues, the first being what is the clinical relevance of effects being seen, and discussion didn't convince me of clinical relevance. Is the effect consistent across secondary endpoints? We didn't see significant effects across the secondary endpoints. What other sort of effects are we seeing? Well, the strongest effects that I could delineate were actually for depression and anxiety and memory loss.

I found it a little bit troubling that there is a variation of opinion about what endpoint we should actually be looking at, whether we should be looking at changes, percent changes, whether we should be looking at counts. I think that was a bit unfortunate that there isn't more consensus about what the most relevant thing we should be looking at in agreement about that, and we could focus on that sort of relevant outcome. I think it would be important to look at.

I'm not convinced that there's no signal here, and I would encourage, I think there are analyses that could be done that are a little bit more robust to some of the challenges we talked about today. I would encourage that those analyses be pursued.

But I never reached that reasonable assurance. I had enough concerns that I didn't reach that level.

DR. HURST: Thanks, Dr. Evans. Dr. New.

DR. NEW: I voted for approvable with conditions because, for one, with the outlier data removed, that the study did reach statistical significance and, for two, as I mentioned in the general discussion, I think the main limitation to the study, it was a short blinded period, and the fact that the surgery itself has a positive beneficial effect on patients, and despite that, they were still able to show a positive result, which is fairly amazing, and I'm willing to credit them a bit for the fact that the implantation of the device has a positive effect as well as turning the device on.

DR. HURST: Thank you. Dr. Petrucci.

DR. PETRUCCI: I voted for approval with conditions because I feel that this general group needs further assistance. Number one, they live in a storm and have endured a very difficult development as well as lifestyle, and any instrument that can be used at this point to assist them, despite the p-values, for significance in some areas, I think should be considered as supportive evidence to help this population.

DR. HURST: Thank you. Dr. Engel.

DR. ENGEL: I voted for, four reasons: one, because I didn't see any safety issues; two, I thought it was unreasonable not to exclude the outlier given the circumstances of just two days; three, I think month four demonstrated to me that the effect of surgery was wearing off in the control group, and that's the reason why the results weren't better than they were; and four, because I have great compassion for this patient group who have nothing else.

DR. HURST: Thank you. Dr. Good.

DR. GOOD: I voted against primarily because although there was a statistically significant difference between the experimental and control group, at the end of the blinded period, I felt the blinded period was too short. I still was not convinced about the clinical relevance of the trial. I think that the long-term follow-up is encouraging, but I don't think that we can make any decision based on that alone. I think probably with the conditions we put on, the device is reasonably safe, and I'm willing to go along with that aspect.

DR. HURST: Thank you. Dr. Barker.

DR. BARKER: I think, taken as a given, that all the Panel members want very badly to help this patient population. I think that the evidence suggested a statistically significant, but minimally clinically significant, short-term effect as well as a much more clinically significant but much less reliably measured long-term effect, and I think the safety was adequately demonstrated.

I think what was also demonstrated is that the FDA should act quickly to set the bar higher for future designers of trials in this area so that future Panels aren't placed in the same quandary that we've been.

DR. HURST: Dr. Paolicchi.

DR. PAOLICCHI: I voted against approval with conditions because I feel similarly to Dr. Evans, that although we all feel tremendous compassion for this population, we certainly don't want to expose them to procedures that may not have a reasonable benefit for them. We don't know yet what that group is. We don't really know what their outcome would be. We don't yet know what group will be most benefited by it, and there are concerns overall, not in terms of its safety, but the fact that this device does carry multiple surgical risks, multiple surgical procedures, and in some ways should have greater efficacy given those risks.

DR. HURST: Dr. Chugani.

DR. CHUGANI: Yeah, I voted for approval with conditions for a number of reasons, some of which Dr. Engel has voiced. This group is in desperate need. I was impressed with the fact that 80 percent of the patients said they would do it again, and I think that has to be given some weight, and that factored in for me quite a bit.

DR. HURST: Dr. Ravina.

DR. RAVINA: I voted against approval for the same reasons. Again, I think we all understand the need, and I think this patient population is in desperate need and deserves a therapy with a reasonable standard of evidence of efficacy that I don't believe we've met. I think Dr. Evans laid out the statistical concerns as well as the issues about clinical meaningfulness, and we have to take both of those in perspective, and we're unsure about efficacy over three months in a chronic condition with a surgical therapy. I think it's really setting a very low bar for approval, and I think it's going to be hard for the Agency to undo, to set a higher bar if they approve based on this level of evidence.

DR. HURST: Thank you. Would the Industry or Consumer Rep have anything to say?

MS. PETERSON: No, thank you.

MR. HALPIN: No, thank you.

DR. HURST: Okay. I'd just like to thank all the Panel members for their very hard work both before they came here today as well as today. It was quite obvious that people were very familiar with this study, and it's extremely, as we're all aware, very, very complicated study to understand and a very difficult decision to make.

Lastly, I'd like to thank the Panel, the FDA, and the sponsor and, Dr. Eydelman, do you have any comments?

DR. EYDELMAN: I just wanted to thank once again all the Panel members and especially Dr. Hurst for a very thoughtful discussion today. We appreciate your time and your commitment to the process.

DR. HURST: Thank you. The March 12, 2010 meeting of the Neurological Device Panel is now adjourned.

(Whereupon, at 5:58 p.m., the meeting was adjourned.)

C E R T I F I C A T E

This is to certify that the attached proceedings in the matter of:

NEUROLOGICAL DEVICES PANEL

March 12, 2010

Gaithersburg, Maryland

were held as herein appears, and that this is the original transcription thereof for the files of the Food and Drug Administration, Center for Devices and Radiological Health, Medical Devices Advisory Committee.

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Official Reporter